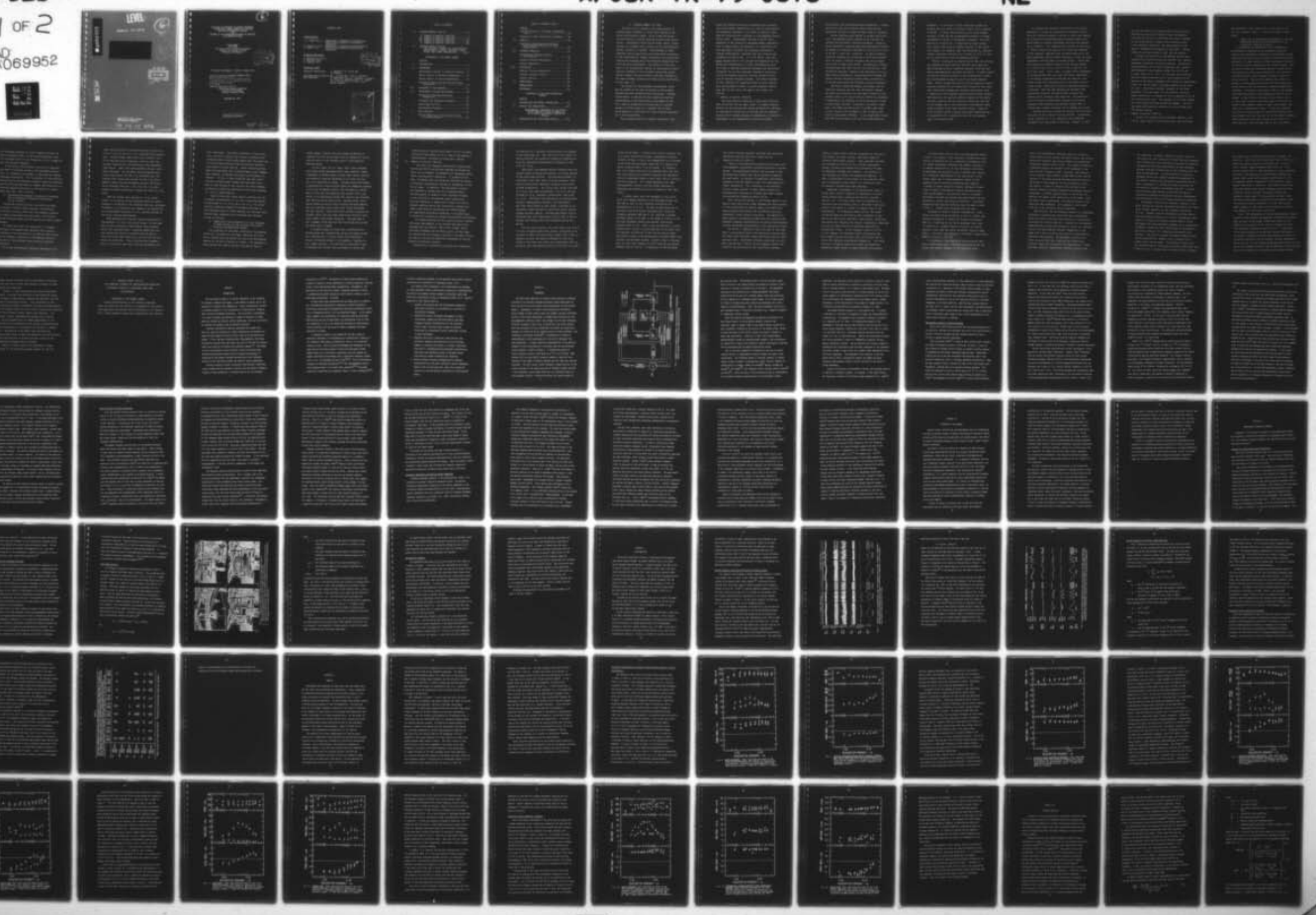
AD-A069 952 KENTUCKY UNIV LEXINGTON WENNER-GREN RESEARCH LAB F/G 6/5
THE CAUSES OF DECREMENTS IN AIRCREW PERFORMANCE: PHYSIOLOGICAL --ETC(U)
SEP 78 C F KNAPP, J M EVANS, D R RANDALL F44620-74-C-0012
AFOSR-TR-79-0676 NL

UNCLASSIFIED

1 OF 2
AD A069952



LEVEL II

AFOSR-TR- 79-0676

AD A069952

DDC FILE COPY

DDC
RECEIVED
JUN 14 1979
C

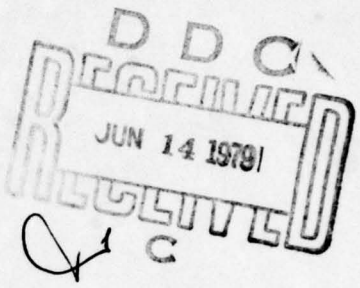
Approved for public release;
distribution unlimited.

79 06 12 070

(6)

THE CAUSES OF DECREMENTS IN AIRCREW PERFORMANCE: PHYSIOLOGICAL CHANGES PRODUCED BY VIBRATION AND OTHER ENVIRONMENTAL STRESSES AND RESPONSE OF THE CARDIOVASCULAR SYSTEM TO VIBRATION AND COMBINED STRESSES

FINAL REPORT
1973-1978
Air Force Office of Scientific Research
Contract No. F44620-74-C-0012
University of Kentucky



Principal Investigator: Charles F. Knapp, Ph.D.

Wenner-Gren Research Laboratory
University of Kentucky
Lexington, Kentucky 40506

September 20, 1978

408 012

RESEARCH TEAM

Investigators

C.F. Knapp Ph.D., Department of Mechanical Engineering, Wenner-Gren Biomedical Engineering Laboratory
D. Randall, Ph.D., Department of Physiology and Biophysics
J. Evans, M.S., Wenner-Gren Biomedical Engineering Laboratory

Graduate Assistants

A. Bhattacharya Ph.D.
J. Marquis, Ph.D.
E. Frazier, M.S.

Technical Staff

Surgical Technicians: C. Woolfolk, D. Cloyd and D. Graham

Instrumentation Specialists: B. Stanifer; and R. Stanback

Data Analysts: T. Geoffroy, B.S.; C. Fischer, T. Lowery M. Jones; M. Vannier, M.D.: C. Young, M.S.; G. Hirsch; S. Proffit, B.S.; and B. Waters

TABLE OF CONTENTS

TABLE OF CONTENTS (CONT.)

A. PROGRAM SUMMARY 1973-1978

The goal of this program is the understanding of cardiovascular responses to force-field loading of the intact physiological system. Force fields may be due to earth gravity or forces produced by whole body acceleration. Acceleration forces may be either static, slowly varying, or extremely fast relative to the cardiovascular system's capacity to respond. Understanding of these responses implies qualitative and quantitative evaluation of the cardiovascular changes produced by the acceleration loading and knowledge about the mechanism responsible for eliciting these adjustments. Our efforts in the early phase of the program were limited to investigating cardiovascular responses to high frequency whole body acceleration (2-30Hz), but more recently have been extended to the domain between sustained and time-varying acceleration of less than 1 Hz.

The effects of time-dependent acceleration stress may be evident at the time of exposure or may produce delayed reactions through chronic alterations. Maximum effectiveness in meeting military objectives requires understanding of the physiological adjustments to the full range of acceleration stresses and is a problem unique to military medicine in general and to aerospace medicine in particular for those stresses encountered in flight operations.

This program focuses on a general plan which inte-

grates the advanced analytical techniques and instrumentation development capabilities of a team of physiologists and biomedical engineers in an effort to develop a data base for cardiovascular responses to time dependent acceleration stress. Measurements from the invasive instrumentation of the chronically implanted animal preparation used in these studies are essential for identifying the most meaningful variables for assessing acceleration-induced cardiovascular responses when less invasive measurements are made on man. It is our belief that this basic research effort will provide the background for the design and implementation of human investigations which will lead to improved protective equipment and operational procedures for military personnel exposed to the acceleration environments resulting from the optimal utilization of advanced aerospace systems. Our efforts devoted to this rationale are summarized below for each contract year and presented in detail in yearly progress reports from 1973 to 1977 and in the body of this report for 1977-78.

I. Summary of Results (1973-74)

The cardiovascular responses to whole body vibration were classified into two major types: 1) changes produced directly by the applied time varying acceleration, mediated by biomechanical properties of the body and its component systems and 2) changes produced by compensatory or adaptive adjustments to the biomechanical alteration through

physiological and pschyophysiological mechanisms. Studies during this year were directed toward exploring the mechanisms involved in these two major types of response.

Stress responses were studied in acutely and chronically instrumented canines exposed to G_z vibration on vertical and horizontal vibration platforms. Vibration tests consisted of exposing awake and anesthetized animals to sequential sinusoidal vibration of 2-30 Hz at 0.5-3.0 G at 30 sec., 2 and 5 min. intervals. In some procedures, vibration frequency was varied and G level held constant while in others, vibration frequency was held constant and G level or peak force varied. The measured variables included heart rate (HR), aortic flow and pressure, left ventricular pressure, coronary flow, myocardial (A-V) O_2, whole body O_2 consumption, transmitted force between the subject and the vibration platform (PNF), acceleration of various body organs and vibration platform parameters.

The force transmitted between the subject and the vibration platform, and the time relationship between the heart and vibration cycle have been isolated by this research effort to be two of the most effective parameters in determining the response of the cardiovascular system to whole body vibration. Previously, increases in mean heart rate (MHR) and mean aortic flow (MAF) were found to vary linearly with increases in PNF divided by the animal's body weight (PNF/BW). It was established further that MAF varied linearly with the log of MHR/Vibration

Frequency. In this year's study, whole body oxygen consumption was also found to increase linearly with increases in PNF/BW. A linear relationship was also found between increases in MHR and the corresponding increases in oxygen consumption as values of PNF/BW were increased. The tests were run at 3 and 12 Hz. A comparison of these results with results from exercise studies reported in the literature suggest, for example, that 3 Hz sinusoidal G_z vibration (animal restrained vertically) at G levels of 0.25 to 1.25 G may be classified as light to moderate exercise.

Efforts to evaluate the sensitivity of the time relationship between the heart and the vibration cycle have also been conducted using an integrated approach involving both animal experimentation and modeling studies. In these studies the passive hydraulic aspects of the cardiovascular system were investigated through the use of an analog computer model. Results showed that aortic flow and especially aortic pressure waveforms can be dramatically altered by the proper time relationship between the vibration and cardiac cycle. A comparison of the computer studies with the animal studies indicated that the passive hydraulic aspects of the cardiovascular system at the very most can account for only 25% of the changes seen in the chronically instrumented, awake animals exposed to the same vibration stress. These results provided further evidence that neural mechanisms may be responsible for a substantial part of the responses seen in the awake animal.

To evaluate the relative contribution of the neural mechanisms in producing cardiovascular responses associated with vibration exposure, a series of tests were conducted in which various pharmacological blocking agents were administered to animals restrained vertically and exposed to G_z vibration. The cardiovascular response of conscious or lightly tranquilized dogs to this stress was compared to the response obtained after the administration of the beta sympathetic blocking agent Propranolol or/and the parasympathetic blocking agent, atropine sulfate. Eleven dogs were exposed to graded increases in PNF through changes in G levels from 0.25 to 1.25 G in 0.25 G steps at 3 Hz for 5 min. each. In all cases, a graded, direct dependence of increasing MHR, MAF, and total peripheral conductance on increasing acceleration amplitude was observed, with stroke volume (SV) increasing only at the higher acceleration values. Mean aortic pressure remained essentially unaffected. When the same sequence was repeated after propranolol blockade, the MHR and MAF increases were blunted and SV increases were amplified. The administration of atropine sulfate alone produced the following responses: MHR increases were markedly damped, MAF increases were slightly elevated, and SV changes were large.

Studies were also initiated to quantify the distributed nature of the vibration forcing function. Transmitted force, important as it is, represents the integrated response of all subsystems of the body. However, it does

not provide specific information about the force being received by a particular internal organ--information which may be the key to explaining the overall response of the cardiovascular system to the vibration stress. It was reasoned, therefore, that measurements of the specific biomechanical response of individual internal organs may provide further insight into the problem.

Acutely and chronically instrumented canines were exposed to G_z vibration using the vertical and, recently completed, horizontal vibration platforms. Acceleration transmissibility of the heart, diaphragm, and sternum were measured in the frequency range from 2-30 Hz and G levels from .75 to 1.5 G. For the same dog restrained both horizontally and vertically, the transmissibility modulus of the heart, diaphragm, and sternum was considerably higher for the horizontal case when compared to the vertical case. The primary resonant frequency of the three anatomical sites was higher for the vertical vibration mode; occurring at a frequency of 4-5 Hz compared to 3-4 Hz for the horizontal case. The response of all three anatomical sites beyond 10 Hz was essentially damped. The findings were preliminary and served as an initial data base for further studies.

II. Summary of Results (1974-75)

During this contract period vibration studies in the 2-30 Hz range, begun in the previous year, were continued

and concluded (1 and 2 below) and a pilot study in the very low frequency range (< 1 Hz) was initiated (3 and 4 below).

1. Comparison of Cardiovascular Responses in Canines Restrained Vertically and Horizontally to G_z Sinusoidal Vibration (2-20 Hz)

To delineate the influence of $+G_z$ orthostasis on cardiovascular responses to G_z sinusoidal vibration, studies were performed on chronically instrumented canines restrained horizontally with respect to earth gravity and exposed to the same protocol as those restrained vertically in previous studies conducted on the vibration table. The principal finding was the marked decrease in mean aortic flow response to whole body vibration for the canines restrained vertically when compared to those in the horizontal position. The vertical subjects were shown to markedly increase mean aortic flow with increasing transmitted force, while the horizontal subjects showed minor increases. Increases in mean aortic flow for the animals restrained horizontally were produced principally by increases in heart rate in contrast to the vertical case in which some increased their mean aortic flow mainly by stroke volume changes, others by heart rate changes, and others by a combination of both. It was also observed that control stroke volume for the vertical subjects was approximately 40% less than that of the horizontal subjects. These decreased values were thought to be a result of blood pooling in the periphery due to the +1 G_z ortho-

static loading. The combined stress of $+G_z$ orthostasis and G_z vibration appeared to produce a more sensitive cardiovascular system capable of responding with larger changes in mean aortic flow that those seen with G_z vibration alone.

2. Acceleration Transmissibility of Internal Organs in Canines Exposed to Whole Body Vibration (2-12 Hz)

Studies to measure the G_z acceleration transmissibility of individual organ systems begun in the previous year were concluded during this contract period. The experimental protocol was essentially the same as that described above. The preliminary data base of the previous year was enlarged and refined.

A closely fitting family of transmissibility modulus (TM) curves for the various G levels employed was obtained by normalizing the absolute organ acceleration by the measured table acceleration. It was found that the TM of the diaphragm, heart and sternum tended to be higher for the horizontal cases than for the vertical cases: as much as 90% higher for the peak response of the heart and diaphragm. The primary resonant frequency for the three anatomical sites was higher for the vertical vibration mode occurring at a frequency of 4-6 Hz compared to the 3-4 Hz for the horizontal case. The response of all three anatomical sites beyond 10 Hz was essentially damped.

Transmissibility phase angle (TPA) was similar for both the horizontal and vertical vibration modes. Heart

and diaphragm appeared to "track" together through the entire frequency range. At all three anatomical sites, TPA increased from 0 at low frequencies (2 Hz) through 90° near the resonant frequency.

In one animal intra-thoracic pressure was measured and found to correlate directly with diaphragm acceleration, i.e. tending to be greater in amplitude for greater diaphragm acceleration. The fluctuations in intra-thoracic pressure due to the diaphragm "pumping" caused by vibration were of sufficient amplitude to suggest the possibility of vibration-induced alterations in the dynamics of venous return and right atrial filling.

3. Cardiovascular Response of Canines to Sustained and Low Frequency Sinusoidal Acceleration (up to 0.05 Hz)

During the contract period a new effort was begun in response to concern about potential cardiovascular difficulties resulting from ultra-low frequency acceleration loading associated with high speed, low altitude, terrain-following flight and the execution of aerial combat maneuvers.

To conduct the study, an existing 50 ft. diameter centrifuge in the Wenner-Gren Laboratory was prepared. The purpose of the experiment was to quantify mean cardiovascular changes in chronically instrumented canines as a function of sustained and slowly-varying sinusoidal acceleration.

All of the cardiovascular responses measured in the

study were qualitatively and quantitatively similar for a 0 to +1 G_z tilt and 0 to +1 G_z sustained centrifugation test. Stroke volume, mean aortic flow, systolic, diastolic and mean aortic pressures, systolic right ventricular pressure and left ventricular dP/dt decreased from control. Heart rate and peripheral vascular resistance increased. All variables which decreased their values from control for the +1 G_z sustained test, decreased their values even further for the +2 G_z tests. However, heart rate and peripheral vascular resistance which increased from control for the 0 to +1 G_z test showed no further significant increase for the 0 to +2 G_z tests.

When the animals were exposed to a +2 G_z stress after a +1 G_z control period (produced either by centrifugation or orthostasis) the responses were less consistent. Prolonged +1 G_z orthostasis was thought to be responsible for the decreased responses to +2 G_z loading observed in the aortic pressure measurements.

When acceleration stress was varied sinusoidally at approximately 1,2, and 3 cycles per minute (at the same peak to peak acceleration amplitude as those produced during the sustained tests), responses meaned over the test period were found to correlate with the mean G level during the test period only, and not with the frequency of oscillation. Those variables which showed a lack of correlation were heart rate and peripheral vas-

cular resistance. The rates of decrease in mean aortic flow, and aortic systolic and diastolic pressures with increasing mean G levels were greater when the animal was in the horizontal position than the vertical position with respect to earth gravity. Stroke volume responses which also decreased with increasing mean G were independent, however, of whether the animal was horizontal or vertical. In fact, stroke volume was the only cardiovascular variable whose changes were consistent from test to test and dog to dog, and was the least affected by the way in which the acceleration stress was produced, i.e. tilt or centrifugation.

Taken collectively, these results indicate that for sinusoidal accelerations of 1,2, and 3 cycles per minute at amplitudes of 0 to +2 G_z and +1 to +2 G_z, the cardiovascular system was capable of following with peak to peak responses equal to those obtained for sustained tests and with mean responses which correlate with the mean G level of the test.

4. Comparison of the Orthostatic (+1 G_z) Tolerance of Awake Canines to that of Normal and Cardiovascularly Deconditioned Humans

The usefulness of the awake, chronically instrumented canine as a surrogate for man under conditions of orthostatic loading along the spinal axis was also investigated because of the data collected in 3 above. The response of these canines was found to be much the same as that of

normal humans, however there was enough difference to indicate that the canine might also be studied as a surrogate for man in a non-extreme state of cardiovascular deconditioning.

In this study, for all tests, heart rate increased and stroke volume decreased which, when combined, showed a decrease in cardiac output in each case. Aortic systolic and diastolic pressures decreased in all tests but one, and in it there was no change. Coronary blood flow showed a characteristic time-variation where the immediate response to tilt was increased coronary flow followed by a decrement in flow over the remaining test period, with a net result of no appreciable change from control when averaged over the five minute test period. Maximum dP/dt consistently showed an initial sharp increase followed immediately by a decrease below normal that lasted throughout the test session. Right ventricular systolic pressure decreased, while left and right ventricular diastolic pressures showed inconsistent responses. The magnitude of the T segment of the ECG over the five minute test period was often seen to change.

A response common to normal man, cardiovascularly deconditioned man, anesthetized canines and awake canines was a 40% decrease in stroke volume with orthostatic stress; differences appear in the subjects' response to this common decrease. The noninvasive orthostatic index of Burkhart and Kirchoff was calculated for normal and

cardiovascularly deconditioned humans and for the awake canines and does appear to be an index of the degree of cardiovascular tolerance to orthostatic loading.

III. Summary of Results (1975-76)

The ultra low frequency acceleration studies begun during the 1974-75 period were expanded and became the basis for a systematic investigation of integrated batrostatic cardiovascular regulation. To accomplish this goal, the Wenner-Gren centrifuge was modified to produce ± sinusoidal acceleration loadings at frequencies in the 0-2 Hz range. In addition, the experimental protocol was expanded to include the use of pharmacological blocking agents to produce a total autonomic blockade in the chronically instrumented animal preparation. With this addition, a comparison of normal and totally blocked responses during the acceleration loadings provides a data base for evaluating the "effectiveness" of compensatory barostatic mechanisms in counteracting, or minimizing acceleration-induced pressure/flow disturbances.

The changes made during this contract period, coupled with major improvements in our digital data aquisition (Raytheon 704) and analysis (PDP 11/10) systems, which continued throughout the following years, set the stage for quantifying the frequency response of the major cardiac and vascular baroreflex mechanisms responding to time dependent acceleration loadings.

Specifically, acceleration loadings were produced by

the addition of a rotatable platform which was attached to the centrifuge arm. With the aid of this slowly rotating platform, the system was capable of producing up to ± 3 G_z sinusoidal acceleration at frequencies from 0.001 to 1.8 Hz.

Chronically instrumented canines (tranquilized with Innovar) were restrained horizontally in a couch mounted to the centrifuge platform. The measured variables include heart rate, ECG, aortic flow and pressure, right and left ventricular pressures, coronary flow and centrifuge acceleration. The initial test series consisted of a +2 G_z step input acceleration (1 to 2 G's per sec) followed by ± 2 G_z sinusoidal accelerations from 0.005 to 1.8 Hz. Individual and combinations of pharmacologic blockers (Phentolamine, Atropine, and Propranolol) were then admisistered to each animal, producing an experimental state from which a particular neural control pathway had been removed. Fourteen experiments using 8 unblocked dogs and 2 experiments using 2 dogs in the unblocked and blocked states were conducted during this period.

For both the +2 G_z and -2 G_z step inputs, the initial (2-5 sec) responses were often similar, consisting of an increase in heart rate and cardiac output, with a drop in apparent vascular resistance, although for the +2 G_z (blood to the feet) case there was a hydrostatic drop in pressure, with the opposite being true for the -2 G_z case

(blood to the head). Following this initial response, the +2 G_z tests consistently evoked a sympathetic response (further increase in heart rate accompanied by an increase in max dP/dt and resistance) resulting in a recovery of aortic pressure within 15 to 20 seconds. In contrast, the -2 G_z steady state with its elevated aortic and left and right ventricular diastolic pressures was characterized by a pronounced rhythm in heart rate, and all pressure and flow variables. This rhythm appeared to be under parasympathetic control, and was established both in magnitude and periodicity within 10 seconds of the input stress.

In almost every case, the frequency of the cyclic heart rate changes observed in the unblocked animals was the same as that of the sinusoidal acceleration for frequencies up to 0.3 Hz. The peak to peak amplitude of the heart rate oscillations increased with increasing frequency between 0.005 and 0.1 Hz, reaching a maximum (average change of 127 bpm) in the range of 0.02 to 0.1 Hz, and then decreased rapidly with minimal oscillations observed after 0.3 Hz. Peak to peak oscillations in aortic pressure were similar to those observed for the heart rate, with maximal oscillations in the 0.03 to 0.06 Hz range. Preliminary results using pharmacologic blockade (heart rate constant and periphery blocked, 'hydraulic dog') indicated that the open loop response of aortic pressure was maximal between 0.04 and 0.06 Hz. A comparison of the unblocked

and totally blocked responses indicated that peripheral mechanisms were operative up to about 0.03 Hz.

IV. Summary of Results (1976-77)

Studies of cardiovascular regulation associated with time dependent acceleration continued during this contract period. The experimental protocol was the same as that described above except that the acceleration frequency was kept below 1 Hz because of undesirable acceleration gradients along the animal's spinal axis associated with higher frequencies. This limitation in the technique was not a major problem in these studies because all cardiovascular responses of interest were highly damped at acceleration frequencies above 0.25 Hz.

Also, during this period, a significant advance in our digital data acquisition system (Raytheon 704) made possible on-line calculations of cardiac output, the arterial-to-venous pressure drop across the circulation, and, most importantly, total vascular resistance. The addition of total vascular resistance provided data for evaluating the frequency response characteristics of cardiac and peripheral vascular mechanisms participating in the regulation process.

The variables measured in the first part of the study (Part I) consisted of aortic flow and aortic pressure (AP), left ventricular pressure, right ventricular pressure (RVP), and heart rate. Calculated variables, available on a one-beat, delayed basis from an on-line computer system, consisted of the derivative of left ventricular pressure

(dP/dt), cardiac output (digital integration of the aortic flow signal) and total vascular resistance [(mean AP-diastolic RVP)/cardiac output]. Total autonomic blockade was achieved by infusion of the α blocker phenoxybenzamine, followed by β blockade with propranolol followed by cholinergic blockade with atropine. The efficacy of this blockade was tested with appropriate agonists. To date, 22 experiments using animals in the reflexive state and 12 experiments using animals in a particular state of autonomic blockade have been conducted.

Responses from animals in the nonreflexive state indicate that a passive (hydraulic) attenuation of acceleration-induced aortic pressure oscillations occurred above 0.1 Hz. This would imply that the attenuation of the heart rate oscillations seen in the normal (reflexive) state in this range is a result of reduced input to the baroreceptor. At frequencies below 0.03 Hz, the normal (reflexive) mean AP oscillations were attenuated in comparison to the passive (hydraulic) oscillations, indicating that below this frequency the vascular compensatory mechanisms are able to reduce pressure disturbances generated by acceleration stress. In the frequency range of 0.03 to 0.1 Hz, however, the reflexive animal consistently had much larger pressure and heart rate oscillations than at any of the remaining acceleration frequencies. This would indicate a frequency range within which the regulatory mechanisms appear unable to reduce pressure disturbances.

A second study [Part II] was initiated because efforts in Part I to produce a total autonomic blockade were hindered by an apparent loss of α adrenergic blockade any time a β and/or cholinergic antagonist was added: evidence of a complex interaction of α,β and cholinergic activities. An experiment was designed to use a standard test dose of an α stimulator administered to the same animal in the normal state, and in three subsequent states in which separate putative buffering mechanisms were removed: 1) normal 2) heart paced [to prevent a decrease in heart rate] 3) paced +β blockade [to prevent decreased heart rate and peripheral β vasodilation] and 4) β blockade + cholinergic blockade [to prevent decreased heart rate and peripheral β and/or cholinergic dilatation]. The animal preparation and measured variables were the same as those in Part I. Studies were conducted using ten dogs.

Increases in arterial pressure produced by α stimulation activated reflex peripheral as well as cardiac compensatory mechanisms to reduce the pressure disturbance. That is, in addition to the reflex decreased heart rate, in response to α receptor mediated increases in arterial pressure, there were two reflex peripheral vascular components, β adrenergic and sympathetic cholinergic vasodilation.

V. Summary of Results (1977-78)

The systematic investigation of cardiovascular regulation during whole body, sinusoidal acceleration was continued with special emphasis on the following areas.

First, the acceleration frequency range was limited to values below 0.25 Hz because the major cardiac and vascular baroreflex responses were highly damped for acceleration frequencies greater than 0.10 Hz. This change allowed for a detailed analysis to be made of the responses in the most critical frequency range. Secondly, with advances in our digital, data analysis system (PDP 11/10), Fourier analysis of the data provided the magnitude and phase relationship of the responses to the acceleration stress. And lastly, in order to identify that portion of the totally reflexive response produced by peripheral vascular mechanisms, a further sophistication of the animal preparation was added; total denervation of the heart. With the heart totally denervated, the combined effect of the alpha and beta adrenergic, and sympathetic cholinergic activity in the periphery can be identified.

Specifically, the low frequency dynamics of integrated, barostatic cardiovascular regulation were investigated, using sinusoidal whole body acceleration as a noninvasive cardiovascular forcing function. Chronically-instrumented, unanesthetized canines were exposed to spinal axis acceleration of $\pm$ 2G amplitude at discrete frequencies in the range from 0.008 to 0.25 Hz, and specific cardiovascular responses were measured. The measured variables were aortic pressure and flow, right and left ventricular pressure, heart rate and spinal axis acceleration. These data were digitally sampled and filtered, at which time

two additional variables, effective systemic vascular resistance and left ventricular stroke flow were computed. The filtered data were then Fourier analyzed to determine the magnitude and phase relationship of the responses between selected variables and of each variable with respect to acceleration. The participation of neurally-mediated cardiac and vascular baroreflex mechanisms in the overall response was evaluated by comparing the subjects' responses in a reflexive (neurally active) and non-reflexive (neurally blockaded) condition. Transfer functions were then derived to describe the passive acceleration-induced intravascular pressure disturbances and the control action of the major baroreflex mechanisms.

The dynamic (oscillatory) frequency response of the major cardiac and vascular baroreflex mechanisms was found to be limited primarily to the frequency range below 0.10 Hz. Systemic vascular resistance exhibited significant oscillatory behavior up to 0.04 Hz, decreasing thereafter to a minimal oscillatory response above 0.14 Hz. Coincident with this amplitude response, was a progressive increase in phase lag, both with respect to acceleration and aortic pressure, for increasing acceleration frequencies. The overall systemic resistance response could not be accounted for, however, with a simple first or second order control model. The response of heart rate was characterized by increasing oscillatory amplitudes from 0.008 Hz up to a resonant peak at about 0.06 Hz, followed

by progressively decreasing oscillations at higher frequencies. Heart rate oscillations were roughly 180° out of phase with aortic pressure oscillations up to 0.03 Hz, with a further lagging tendency above 0.03. Hz. With aortic pressure and its time derivative as input variables, the heart rate response was satisfactorily modeled as a second order system with a damping coefficient of 1.24, an undamped natural frequency of 0.075 Hz and an input/output time delay of 0.626 sec. Oscillatory stroke flow amplitude changes were largely frequency-invariant from 0.008 to 0.25 Hz, and were influenced primarily by changes in right heart filling pressure and heart rate. The phase relationship of stroke flow to diastolic right ventricular pressure indicated a 2.18 sec time lag between changes in right heart filling pressure and resultant changes in left heart stroke flow.

A 30 - 35% attenuation of passive acceleration-induced arterial blood pressure disturbances (non-reflexive responses) was seen in the normal (reflexive) state for frequencies up to about 0.07 Hz, with no evidence of effective barostatic regulation above 0.10 Hz. A comparison of the participation of cardiac and vascular mechanisms in the overall responses indicated that barostatic control is achieved principally via the systemic vascular mechanisms below 0.02 Hz, via the cardiac mechanisms from 0.04 to 0.10 Hz, and by the combined action of the two between 0.02 and 0.04 Hz. Due to the interplay of the cardiac and vascular control

mechanisms, and the total circulatory (i.e., arterial and venous) disturbances afforded by whole body acceleration loadings, the overall level of barostatic regulation measured in the present study is significantly less than those reported in previous studies of the baroreflex control of arterial pressure.

An analysis of the response of the cardiac denervated animals exposed to sinusoidal $\pm$ 2 G_z accelerations at frequencies of 0.005 to 0.3 Hz has also been performed. In the control state, aortic pressure, arterial-to-venous pressure difference and peripheral vascular resistance were slightly reduced while cardiac output, stroke volume and heart rate were slightly elevated.

The reflexive response of cardiac denervated dogs to the acceleration stress was quite different from that of the reflexive normal dogs' response. The reflexive normal animal was found to be able to minimize oscillation in aortic pressure in the low frequency range with an in-phase increase in peripheral resistance. The reflexive cardiac-denervated animals, however, not only were unable to minimize these oscillations but the oscillations were of considerably greater magnitude: 70 mm Hg across the low to mid frequency range, as compared to the 50 mm Hg oscillations of the non-reflexive animals and the 30 mm Hg oscillations of the reflexive, normal animals. The source of these large pressure oscillations was found to be primarily due to increased cardiac output oscillations simul-

taneous with an elevated value of peripheral resistance during the time in which the hydraulic increase in blood pressure was occurring.

Finally, in both the normal and cardiac denervated animals, in either the reflexive or non-reflexive state, an increase in mean aortic pressure was observed with the onset of acceleration stress. This occurrence in the non-reflexive animals eliminated circulating catecholamines as the probable source of this pressor response and therefore other neurohormonal pressor agents were examined. Preliminary results indicated that plasma renin activity was low and appeared not to change appreciably or consistently with acceleration while plasma volume decreased with acceleration as indicated by an increase in hematocrit. Vasopressin on the other hand, doubled with acceleration stress in both the reflexive and non-reflexive states and was felt to be the principal source of the acceleration-induced pressor response.

Details of these results are presented in three sections in the following progress report for 1977-78.

B. PROGRESS REPORT 1977-78

LOW FREQUENCY DYNAMICS OF CARDIOVASCULAR REGULATION IN CANINES EXPOSED TO SINUSOIDAL WHOLE BODY ACCELERATION

RESPONSES OF THE NORMAL ANIMAL

A detailed description of the research conducted under this phase of the contract is presented in the following pages which constitutes the dissertation of J.A. Marquis, Ph.D., whose graduate studies were supported by the contract.

CHAPTER I

INTRODUCTION

The circulatory system is of primary importance in the transport of nutrients, hormones and oxygen, in the removal of waste, and in the regulation of internal body temperature. Proper cardiovascular control is therefore essential to the preservation of physiological integrity under varied environmental conditions. The circulation is maintained in a state of dynamic equilibrium by a number of pressure or volume sensitive cardiac and vascular control mechanisms, which act principally to regulate the systemic arterial perfusion pressure.

Transient acceleratory loadings associated with normal daily activity, exercise conditions or severe occupational environments are among the most common noninvasive stimuli seen by the cardiovascular system. It has long been recognized that time-dependent, whole body acceleration applied along the spinal (G_z) axis of the body can produce significant arterial and venous blood pressure changes[1-5]. The degree to which the barostatic control network is able to minimize these transient acceleration-induced arterial pressure disturbances is determined by the dynamic response characteristics and integrated function of the individual cardiac and vascular control mechanisms.

Previous studies of neural, barostatic cardiovascular regulation, using a Systems Analysis approach, indicate that the dynamic frequency response of these mechanisms is limited primarily to the frequency

range below 1.0 Hz[6-18]. The majority of these studies examined the response of specific control mechanisms to invasively-applied, localized stimuli using anesthetized animal preparations. Consequently, the application of the results to normal, integrated barostatic control in unanesthetized animals exposed to a more natural stimulus, such as whole body acceleration, is unclear.

To date, whole body acceleration has not been used as a stimulus for investigating cardiovascular regulation, primarily because of difficulties associated with generating significant acceleration levels, >1G, at frequencies below 1.0 Hz by conventional means. In the present study, however, the availability of a specially modified centrifuge made possible the use of whole body $\pm G_z$ acceleration (>1G) at ultra low frequencies (<1 Hz) as an appropriate noninvasive cardiovascular "forcing function" for the study of dynamic integrated barostatic regulation in animals.

In addition to being a novel method for the basic study of barostatic regulation, an investigation of cardiovascular response to low frequency, whole body G_z acceleration, per se, is of practical interest as well. With the recent development and deployment of high speed terrain-following tactical aircraft and blue-water surface effects ships (e.g. hovercraft), operational crew are exposed to a dynamic acceleration environment with a significant frequency content below 1.0 Hz. for extended periods of time[19,20]. While cardiovascular responses to sustained acceleration[1,2,5] and time-dependent acceleration loadings above 1.0 Hz (whole body vibration)[21-23] have been extensively researched and documented, there is little information[24,25]

available concerning responses to, and potential physiological hazards associated with acceleration at frequencies below 1.0 Hz.

The research effort presented in this dissertation was designed to study integrated reflex cardiovascular regulation in unanesthetized, chronically-instrumented canines exposed to sinusoidal whole body spinal-axis acceleration ($\pm$ 2G_z) at frequencies below 1.0 Hz. Specific objectives of the research were to:

1. Quantify the pressure and flow disturbances produced by whole body sinusoidal G_z acceleration as a function of acceleration frequency.
2. Quantify the reflex circulatory adjustments to these disturbances, emphasizing the participation and hence frequency response characteristics of the individual cardiac (heart rate and stroke volume) and vascular (resistance and capacitance) control mechanisms involved in these adjustments.
3. Determine the active (reflexive) versus passive (non-reflexive) response characteristics of the circulatory network, by studying the animals in a normal (reflexive) state and in a pharmacologically-blockaded (nonreflexive) state where the regulatory action of the major neural cardiovascular control mechanisms was inhibited.
4. Develop transfer functions encompassing the response characteristics of the major barostatic control mechanisms, based on this and previous work, which are suitable for inclusion in existing passive (nonreflexive) cardiovascular models.

CHAPTER II

BACKGROUND

The short term regulation of arterial blood pressure is effected principally via centrally mediated barostatic reflex mechanisms for which the aortic arch and carotid sinus baroreceptors are the primary sensors. Adjustments in arterial blood pressure are achieved by reflex changes in both cardiac output and systemic vascular resistance. Control of the cardiac mechanisms is accomplished principally by the parasympathetic efferents (heart rate changes) and the beta adrenergic efferents (changes in heart rate, contractility, and stroke volume), while the peripheral vascular mechanisms (resistance and capacitance changes) are controlled by the combined action of alpha adrenergic and sympathetic cholinergic efferents[26]. Adrenomedullary release of catecholamines to the bloodstream will also elicit responses from these mechanisms. A highly simplified representation of the essential elements of the closed hydraulic circulatory loop and the barostatic control network is shown in Figure 1. A traditional picture of neural barostatic control (from Scher et al.[15]) is as follows: When pressure falls at the arterial pressure receptors, there will be a decrease in the number of sensory impulses per unit time sent into the brainstem. This will cause a reflex decrease in motor activity in the cardiac branches of the vagus nerve and an increase in motor activity in the sympathetic nerve fibers which run a) to the heart and b) to the peripheral vessels, including arterioles, and venous vessels in

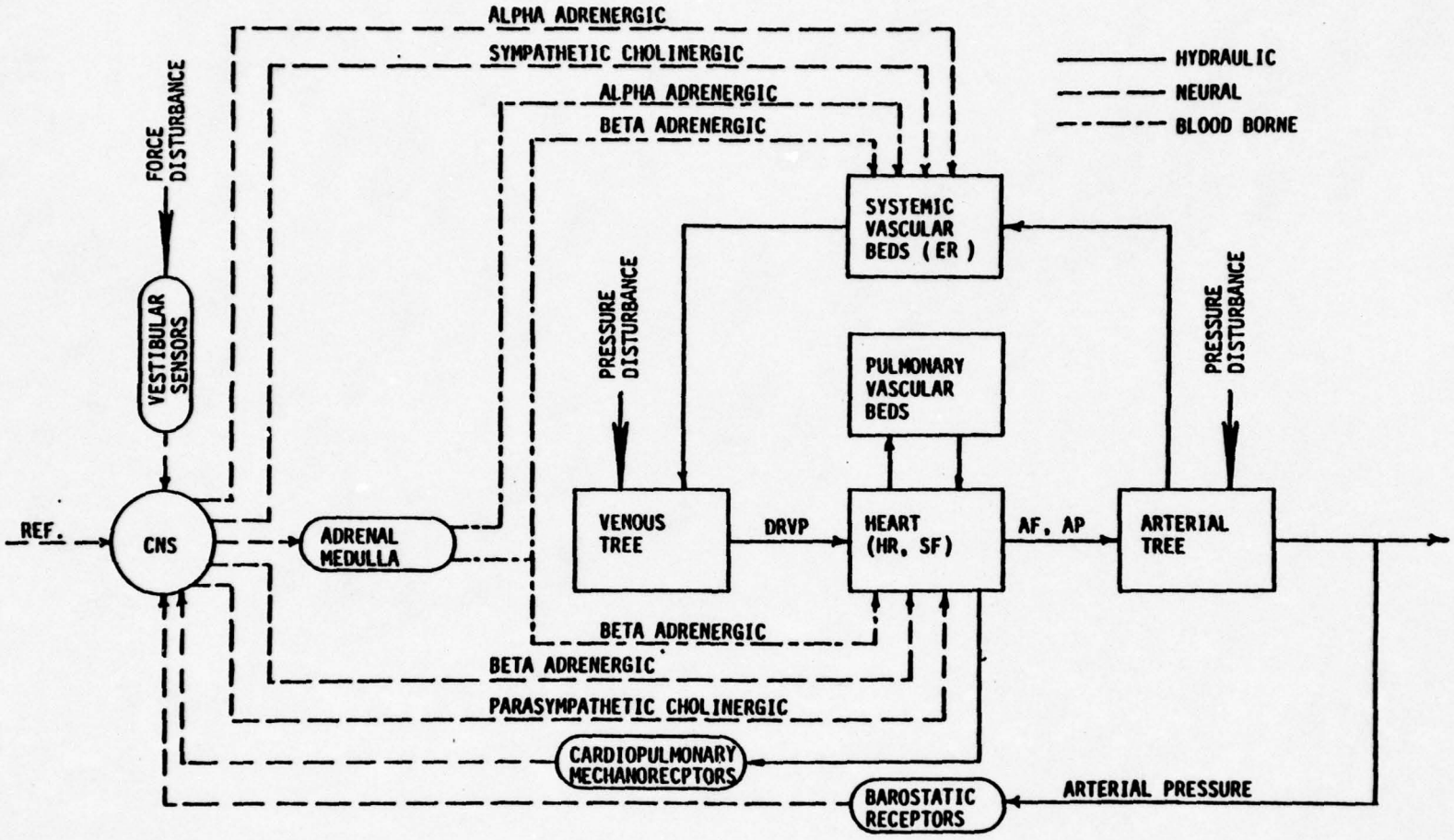


FIG. 1. SCHEMATIC OF THE BAROSTATIC CONTROL SYSTEM FOR RESPONSE TO ACCELERATION-INDUCED PRESSURE DISTURBANCES IN THE CARDIOVASCULAR SYSTEM.

many vascular beds. The decreased vagal firing and increased sympathetic firing will act synergistically to produce an increase in heart rate and an increase in contractility of the heart. The sympathetic discharge to the arterioles will increase peripheral resistance. Constriction of the veins will increase venous return and ventricular filling, leading to an increased stroke volume. All of these factors will tend to increase the blood pressure and counteract the initial change at the baroreceptors. Thus, the neural barostatic control network represents what is classically referred to as a "negative feedback" or compensatory control system.

While the arterial baroreceptors are generally considered to be the primary sensors in the baroreflex network, there are two additional types of sensory input to the central nervous system which have a potential influence on the results of the present study, insofar as they contribute to the overall cardiac and vascular response to whole body acceleration. These are 1) input from cardiopulmonary mechanoreceptors caused by pressure/volume changes in the cardiopulmonary region and 2) inputs from vestibular sensors stimulated by transient forces associated with the applied acceleration stress.

Due to the great abundance of literature in the area of cardiovascular control, a comprehensive review is beyond the scope of this dissertation. The interested reader is referred, however, to several recent reviews of general cardiovascular control from the viewpoint of Systems Analysis (Sagawa, Kumada and Schramm[26]; Guyton, Coleman and Granger[27]; and Sagawa[28]) and integrated central nervous control (Korner[29], and Smith[30]). Since the focus of this dissertation was an investigation of the dynamic response characteristics of the barostatic control

mechanisms, the remainder of this chapter will present a review of literature on central cardiovascular regulation, principally from the standpoint of Systems Analysis, as it relates to the present study. An emphasis will be placed on past work that 1) involved studies of the low frequency dynamics of cardiovascular regulation and 2) will provide a basis for the discussion and interpretation of the present results. Before proceeding, a brief description of the concept of Systems Analysis, its limitations and applications to biological systems is in order.

The Systems Analysis approach is a very general one. A "system" is defined as a collection of components arranged and interconnected in a definite way. The components may be physical, chemical, biological or a combination of all three. A distinguishing feature of the components is that each has an input (stimulus, forcing function, etc.) and an output (response, reaction etc.) and that if the input is varied in a particular way (e.g., sinusoidal pressure pulsation) then the output will vary in a particular way. Ideally the input/output relationship can be expressed in terms of a mathematical equation, having a general analytical solution. Such an equation will include a number of parameters which characterize the functional properties of the component. The overall system is then "built" by a simple linear combination of its individual components. The advantage of this approach is that one should then be able to successfully predict the composite system response to more general stimuli, and for variation in the value of system parameters.

Certain difficulties are encountered, however, when Systems Analysis is applied to biological systems. For example: 1) The identification and functional isolation of individual system components (e.g., specific

neural sensor/effector pathways) is often impossible, 2) System components may have multiple inputs and outputs, some of which can not be controlled or measured (e.g., components of the central nervous system), 3) Some components may exhibit significant nonlinear characteristics such as thresholding, rectification, and directional rate-sensitivity (e.g., arterial baroreceptors), and 4) The integrated function of individual components is not always additive. None the less, Systems Analysis has been, and is, a useful tool for the investigation and quantification of biological control systems where the system under study is operating within a piecewise-linear range or only a linear approximation to the actual control behavior is required.

Baroreceptor Control of Arterial Pressure

Due to the relative ease with which the carotid baroreceptors can be surgically isolated and stimulated, the role of the carotid reflex in control of arterial pressure has been studied extensively using a variety of Systems Analysis techniques.

Scher and Young (1963)[14], in some of their earliest work, studied the effect of pressure pulsation (4-20 mm Hg, at 0.005 - 2.0 Hz) of the bilaterally-isolated carotid sinuses on systemic arterial pressure in anesthetized (choralose), hepranized dogs and cats. Among their findings was one of the more pronounced nonlinearities seen in the baroreflex mechanism, that of "frequency dependent rectification," where the mean systemic arterial pressure was seen to fall with higher pulse frequencies, although mean sinus pressure remained constant. This effect was reported as early as 1952 by Eade et al.[31], in a similar study on cats, and has more recently been verified by Schmidt et al. (1972)[17] and Stegemann and Tibes (1969)[18] for carotid sinus pulsations

between 0.5 and 4.0 Hz, and by Ito (1969)[8] for frequencies between 0.03 and 0.1 Hz. It was shown that this depressor effect derived from an asymetric rate sensitivity, due to properties of the baroreceptors themselves. In the Scher and Young[14] study the reflex arterial pressure oscillations were exactly out of phase with the driving carotid sinus pulsations at the lowest frequencies, then tended to lag progressively more at higher frequencies. The maximum pressure amplification (gain) seen was between 2.5 and 10.0 in cats and 2.0 to 6.0 in dogs. At input frequencies above 0.08 to 0.15 Hz the carotid reflex caused no systemic pressure oscillations (i.e., no compensatory action). Later, Scher et al. (1967)[16] modeled these results as a critically-damped second-order time lag response, with a time constant of 4.0 to 10.0 sec and a 1.0 to 2.0 sec lag. Animals used in this study were vagotomized to remove reflex effects due to the aortic arch baroreceptors. As a result, while there was no vagal input to the heart, sympathetic input remained intact. Oscillatory arterial pressure responses were attributed to reflex action of the periphery, without any specific attempt, however, to measure the possible influence of cardiac mechanisms.

Similar results have been obtained by other investigators, using essentially the same animal preparation. Grodins (1963)[7] determined that the carotid sinus/arterial pressure reflex for input (sinus) frequencies between 0.008 and 0.08 Hz in the anesthetized vagotomized dog could be represented by a critically-damped second-order time lag response, with a gain of 1.8, a natural (corner) frequency of 0.017 Hz and a time lag of 1.5 sec. This corner frequency was considerably lower than those reported by other investigators, but the essential features of the magnitude/phase response were otherwise similar. Grodins also

reported that, while the output (arterial) pressure oscillation were approximately sinusoidal for the vagotomized animal, when the experiments were repeated on non-vagotomized animals the arterial pressure oscillations had a nonsymetrical "double-peaking" response. This non-linearity was attributed to differences in response times of the sympathetic and vagal efferents, and the total participation of cardiac mechanisms in the normal, non-vagotomized response. Similarly Levison et al. (1966)[10], in studies using anesthetized dogs, saw a critically-damped second-order reflex response, with a natural frequency of roughly 0.04 - 0.05 Hz. In this work it was also shown that the superposition of high frequency sinusoids (1.8 Hz) on a slower sinusoidal pressure in the carotid sinuses diminished the amplitude of the reflex response of mean arterial pressure, to a value lower than that obtained for slower sinusoid alone. This additional nonlinear property of the carotid baroreflex response was observed by Scher and Young (1969)[13] as well, in a later study.

Scher et al. (1967)[16] combined Scher's earlier data with those of Levison et al.[10], Grodins[7], and Ito (in Scher et al.[16]) and derived a proportional-plus-derivative sensitive, third-order transfer function from the composite data to describe the frequency response of the carotid sinus/arterial pressure baroreflex mechanism. This transfer function predicted a flat frequency response to approximately 0.05 Hz, followed by a 40 dB/decade attenuation at higher frequencies. The corresponding phase lag was 10° at 0.008 Hz, increasing to a maximum of 145° at 0.16 Hz. The results of these "open loop" studies suggest that, dependent upon overall system gain, some degree of barostatic regulation of arterial pressure is possible via the carotid sinus reflex when arterial

pressure changes are relatively slow (i.e., less than approximately 0.05 Hz).

Due largely to surgical difficulties associated with isolation and stimulation of the aortic arch (and subclavian) baroreceptors, there have been few studies to determine the response characteristics of these receptor areas, or to assess the relative importance of the carotid and arch receptors in dynamic arterial pressure regulation. Allison et al. (1969)[6] investigated the effects of stepwise pressure changes in the isolated aortic arch on cardiac pumping and systemic vascular resistance in chloralose-urethan anesthetized, open-chest dogs. An overshoot-and-recovery type of response in systemic pressure was noted for step changes in arch pressure, indicating that aortic arch/systemic pressure control was higher than first-order in nature. It was concluded that the aortic arch baroreceptor reflex is similar in many ways to the carotid sinus reflex, although there are some quantitative differences between the two. Essentially the same conclusion was reached by Angell-James and Daly (1970)[32] when the carotid sinus and aortic arch receptor areas of open-chest anesthetized dogs were isolated and separately perfused with pulsatile and nonpulsatile pressures. In this study it was found that, when the vasosensory areas were perfused at normal pulsatile pressures and within the normal range of mean pressures, there was no difference in the size of the reflex vascular responses elicited by the same rise in the mean pressure in the carotid sinuses and in the aortic arch. It would seem reasonable to expect, therefore, that the aortic arch and carotid sinus baroreceptors should exhibit similar responses to low frequency stimulation, although this has not been verified experimentally.

Neural Control of Vascular Components

While it was shown, in the studies just reviewed, that the low frequency dynamic behavior of the overall baroreceptor/arterial pressure reflex can be approximated by a critically-damped second-order system, these studies did not demonstrate this as a receptor/effector characteristic for the control of specific vascular (resistance) beds. Ito (1969)[9] and Ito in Scher et al. (1967)[16] reported the effects of carotid sinus pressure changes on blood flow and perfusion pressure in the isolated hind limb of anesthetized and hepranized, vagotomized dogs. The isolated carotid sinuses were pressure pulsed at frequencies between 0.008 and 0.15 Hz while hindquarter flow was held constant, and the resulting changes in perfusion pressure measured. Results showed a flat frequency response to approximately 0.05 Hz with progressive attenuation at higher frequencies and a time delay of 3.0 to 5.0 sec in the output response, indicating a damped, second-order time lag system.

Since normal nervous control of vasomotor tone acts primarily through frequency modulation of an impulse train in individual nerve fibers, the neural control of specific vascular beds can be controlled and studied by stimulating appropriate efferent neural fibers at some center frequency (e.g., 4 Hz) and then modulating the stimulus with a lower frequency (e.g., below 1.0 Hz). Penaz et al. (1966)[12] used this method to study the frequency response of the resistance vessels of the carotid bed in the rabbit, by perfusing one carotid artery at a constant pressure and measuring the changes in blood flow in response to sinusoidal changes in stimulus frequency given to the ipsilateral cervical sympathetic nerve. They found that the oscillatory flow amplitude was constant from 0.016 to 0.05 Hz with an attenuation of about 20 dB/decade

in the range above a corner frequency of 0.062 Hz. The combined magnitude/phase response indicated that the vasomotor response could be described by a first-order delay system with a time constant of 2.5 sec and a transportation lag of 1.5 sec. In the same study Penaz et al. reported essentially the same frequency response characteristics for neural vasomotor control in the femoral arterial and the superior mesenteric arterial beds. Both showed a more prominent resonant peak at about 0.04 to 0.05 Hz, with comparable corner frequencies. In an earlier study Penaz and Burianek (1963)[11] also investigated the dynamic response of the capacitance vessels of the ear in rabbits to a similar frequency-modulated stimulation of the cervical sympathetic nerve. Changes in volume of the ear were recorded by plethysmography and related to frequency. The results differed from those on the dynamics of resistance vessels in several respects: The latency of the venous response (3 sec) was longer than that of resistance vessels and the frequency characteristics appeared to reflect a second-order, rather than a first-order system, as indicated by a greater amplitude attenuation of approximately 30 dB/decade. No clearcut corner frequency was seen within the frequency range covered (0.008 - 0.2 Hz), indicating that the capacitance system has a much slower response than the resistance control system.

The results of these studies on neural control of specific vascular beds suggest that it is appropriate (as most cardiovascular modelers have done) to represent the systemic vascular beds in lumped fashion, where the dynamic response characteristics of the composite representation actually reflect the functional sensor/effector properties of individual neurally-controlled vascular regions.

Neural Control of Cardiac Mechanisms

Since the systemic arterial pressure level is a function of cardiac output, as well as vascular resistance, an understanding of the participation of neurally-mediated cardiac mechanisms in baroreflex control is also important. As noted thus far in this review, the role of vascular mechanisms in the barostatic regulation of arterial pressure has been extensively investigated. Considerably less attention has been paid, however, to the influence of cardiac mechanisms (heart rate and stroke volume), especially from the standpoint of their low frequency characteristics.

The dynamic response characteristics of baroreceptor-mediated heart rate control have been studied in some detail. Reflex changes in heart rate are achieved through combined, but not necessarily additive, sympathetic and parasympathetic (vagal) efferent activity in the heart. One difference between these two efferent mechanisms was reported by Glick and Braunwald (1965)[33] who found that in unanesthetized, conscious dogs parasympathetic control of heart rate predominated in the reflex response to increased arterial pressure, while sympathetic control predominated in the response to decreased pressure. A second difference has been demonstrated by Warner and Cox (1962)[34] who showed that the response time of heart rate to vagal stimulation in dogs was much faster (1.0 to 3.0 sec) than to sympathetic stimulation (10 to 30 sec). These differences in directional sensitivity and response time for the sympathetic and parasympathetic reflex mechanisms result in a pronounced nonlinear, nonsymetrical heart rate response to a symetrical (e.g., sinusoidal) input at the baroreceptors. For example Scher et al. (1972)[15] generated pressure pulsations in the aortic arch and carotid

sinuses of chronically-instrumented, conscious dogs by the sinusoidal inflation and deflation of cuff occluders placed on the ascending and descending aortic arch, and measured reflex changes in heart interval. The response was characterized by a sharp drop in heart rate preceeding the peak of pressure increase, followed by a gradual rise after the peak decrease (minimum) in pressure. A sinusoid was least-squares fitted to the input (aortic arch pressure) and output (heart interval) waveforms, and then the magnitude ratio and phase angle between the two computed. For the frequency range studied (0.06 to 0.25 Hz), the amplitude ratio of heart interval (sec) to pressure (mmHg) was 0.026-0.027 at 0.06 and 0.14 Hz, and 0.017 at 0.25 Hz. There was a progressive phase lag from 0^{o} at the lowest frequency to a value of 40^{o} at the highest. The same experiments were conducted in baboons; and heart rate response to tilt and lower body negative pressure was studied in humans. It was concluded from this comparative study that heart rate control is primarily parasympathetic in the dog, primarily sympathetic in the baboon, and intermediate in man.

The frequency response characteristics of stroke volume regulation have essentially gone uninvestigated. This is probably due to difficulties associated with the experimental isolation, and independent manipulation of those parameters which affect stroke volume. Left ventricular preload and afterload, and cardiac contractility have traditionally been considered the three determinants of left ventricular stroke volume, with the latter being under the direct influence of sympathetic and vagal cardiac innervation[26]. A reciprocal relationship between heart rate and stroke volume is also recognized. Consequently, stimuli that elicit responses from the baroreflex mechanisms will

influence stroke volume changes either directly, in the case of heart rate and contractility, or indirectly, through the relationship of pre-load-afterload conditions to vascular resistance and capacitance activity. Scher et al. (1968)[35] used multiple regression analysis to determine which of a number of cardiac parameters were necessary to construct a predictive model of stroke volume control in conscious, resting dogs. Cardiac interval (time between beats), arterial pressure and left ventricular filling pressure were all found to be significant factors in the accurate prediction of stroke volume, within normal physiological ranges of the variables, although the relative importance of each could not be assessed.

Although indirectly related to left ventricular filling pressure, venous return is an additional determinant of stroke volume (and cardiac output) and should be considered separately because it is probably a better index of systemic venomotor activity. Using a canine heart-lung preparation Herndon and Sagawa (1969)[36] showed a strong proportional relationship between changes in right atrial pressure (venous return) and cardiac output, through the Starling reflex. Because their animal preparation included sectioning of the vagi and constant pressure perfusion of the carotid sinus and brain to inhibit heart rate changes, the reported cardiac output changes actually reflex changes in stroke volume. While the static relationship between venous return and cardiac output is well recognized[36], the transient relationship during moderate short-term changes in venous return or right arterial pressure, is less clear. The traditional view has been that increased cardiac output, for example, is initiated by increased venous return, and that due to a capacitive coupling of the right and left heart through the pulmonary

circuit, inflow into the right ventricle is augmented some finite time before outflow from the left ventricle increases. This notion of a time lag has been disputed by Franklin et al. (1962)[37] in a study of the balance between right and left ventricular output in chronically-instrumented awake dogs. It was reported that mild orthostatic stress induced by a change in posture (horizontal to vertical) caused identical synchronous decreases in right and left ventricular output. On the other hand it was also found that when a more acute change in venous return was experimentally induced by a rapid intravenous injection of saline, a time delay of from 1.5 to 3.0 sec was noted between increases in right and left heart output.

The review, to this point, has been limited primarily to a discussion of the transient characteristics of those neurally-mediated (barostatic) cardiac and vascular mechanisms which should be stimulated by acceleration-induced pressure/flow changes. There are however certain "nonneural" factors which may influence the frequency response of measured cardiovascular variables during whole body acceleration.

Non-Neural Regulation and Passive System Properties

Frequency dependent behavior in the cardiovascular system is not confined to the neural barostatic mechanisms alone. The passive (resistance-capacitance) properties of the various components of the circulatory network and characteristics of the local, "autoregulatory" vascular mechanisms are also a potential source of frequency dependent responses, especially to a global (i.e., total circulatory) stimulus such as whole body acceleration.

The frequency dependence of pressure/flow relationships in denervated vascular beds has been shown by a number of investigators. For example, Bassar and Weiss (1968)[38] analyzed the frequency response of admittance (roughly equal to the flow/pressure ratio) in the isolated rat kidney. Perfusion pressure to the kidney was elevated by steps, and the flow responses Fourier analyzed. The ratio and relative phase of the flow/pressure frequency components were computed, yielding a frequency response representation that indicated an underdamped second-order admittance response for the range from 0.004 to 6.0 Hz. The amplitude ratio had a low frequency minimum at 0.01 Hz and a resonant peak at about 0.2 to 0.4 Hz. This peak and trough in the amplitude response were correlated with flow-autoregulation since they disappeared with the addition of papaverin to the perfusate, which acted to inhibit local vasomotor activity. The admittance characteristics of the cornonary bed in the isolated rat heart were studied in a similar manner by Basser and Weiss, and the results were essentially identical. Penaz et al. (1966)[12] applied step changes in perfusion pressure to the superior mesenteric blood vessels in cats and rabbits and measured resultant flow changes. They observed a second-order underdamped flow response having a resonant frequency between 0.03 and 0.08 Hz. These results were attributed to auto-regulatory mechanisms. More recently Spelman (1975)[39] studied the low frequency (0.007 - 0.1 Hz) admittance characteristics of the external iliac arterial bed in unanesthetized sleeping baboons. An occluder on the common iliac artery was used to preferentially produce sinusoidal pressure or flow oscillations in the iliac bed. Results indicated that iliac admittance could be modeled by an underdamped

second-order system with a resonant minimum at 0.02 Hz. Only small oscillations were measured in systemic arterial pressure and it was assumed that baroreceptor influences were minimal, leading to the conclusion that autoregulatory mechanisms predominated in the measured responses.

One can infer, therefore, that under conditions of noninvasive cardiovascular stimulation or stress (e.g., whole body acceleration), systemic pressure and flow variations will reflect the combined influence of neural baroreflex mechanisms and nonneural factors (autoregulation and passive vascular properties). In order to differentiate these neural and nonneural responses several investigators have compared cardiovascular system dynamics for animals in an intact (neurally reflexive) state and in a state where the action of baroreflex mechanisms has been eliminated, either through surgical denervation or pharmacological blockade. Herndon (1969)[8] studied systemic impedance (ratio of pressure to flow oscillations) in dogs by perfusing the vascular bed with sinusoidally varying flow (0.004 - 0.13 Hz) and measuring the arterial and venous pressure responses. The experimental animal's own heart served as the perfusion pump and an implanted pericardial balloon was used to compress the right atrium thus regulating the desired flow (85% of control $\pm$ 10% oscillation). Arterial impedance exhibited a resonant peak at about 0.067 Hz, only with the baroreceptor reflex intact, whereas the venous pressure response did not indicate any significant difference whether the reflex was intact or not (afferent vagi cut). Taylor (1966)[40] investigated arterial impedance in chloralose-urethan anesthetized dogs in similar low frequency range. He used vagal stimulation with random bursts of stimulation to produce

varying periods of reduced aortic flow. The resulting arterial pressure/flow data was Fourier analyzed to yield a frequency domain representation of arterial impedance. With the baroreflex mechanisms intact, a peak in the impedance amplitude occured between 0.03 and 0.04 Hz, while the impedance amplitude was essentially constant through the entire frequency range (0.004 - 0.13 Hz) with the baroreflex mechanisms removed by a ganglionic blockade. Since pharmacological autonomic blockade and surgical denervation should not influence or alter autoregulatory mechanisms (on a short term basis), the results of these studies suggest that autoregulatory mechanisms do not predominate over central baroreflex mechanisms in the response to large transient systemic pressure or flow changes.

From this review of the neural and nonneural factors which could influence the dynamics of cardiovascular function, it is apparent that pressure/flow disturbances generated by whole body acceleration stress should elicit strong barostatic reflex responses, and that disturbances in the frequency range below 1.0 Hz are of prime interest. Furthermore, as noted in the introductory chapter, while there is an implicit relationship between previous studies of the dynamic behavior of cardiovascular regulatory mechanisms and normal integrated barostatic regulation, the use of low frequency whole body acceleration as a cardiovascular stimulus or "forcing function" should provide information of a more explicit nature.

Several investigators have measured cardiovascular responses to simulated aerial combat maneuvers (SACMs), which are one type of whole body G_z acceleration stress containing a significant frequency content below 1.0 Hz. Although these studies were not designed for

the purpose of investigating barostatic cardiovascular regulation, they do provide some information about integrated cardiovascular function in a dynamic acceleration environment. Erickson and Ritzman (1975)[24] measured heart rate and eye-level arterial blood pressure changes in conscious rhesus monkeys exposed to SACM acceleration stress. Blood pressure changes essentially mirrored (i.e., were reciprocally related to) increases and decreases in acceleration level, with some roudning-off or attenuation where sharp acceleration changes occurred. Heart rate, on the other hand, tended to follow the acceleration level, with an apparent time lag and little response to the high frequency content of the SACM. This type of response supports the idea of the moneky being primarily a sympathetic (i.e., slower) heart rate responder, as noted by Scher et al.[15] Gillingham et al. (1977)[25] measured eye level blood pressure changes in wake humans exposed to SACM and Fourier analyzed the paired input (acceleration) and output (blood pressure) waveforms to then determine an acceleration-to-blood pressure transfer function. It was found that blood pressure changes could be accurately modeled by an underdamped second-order (single zero double pole) transfer function with a resonant frequency at about 0.05 Hz, for input frequencies between 0.005 and 0.2 Hz. No definitive explanation was given for the resonant behavior however. These studies demonstrate that low frequency whole body acceleration is capable of producing significant transient responses in the cario-vascular system, and should represent a suitable stimulus for a systematic study of the dynamics of integrated cardiovascular regulation.

CHAPTER III

STATEMENT OF THE PROBLEM

Several factors relating the the experimental design or methodology utilized in previous studies of dynamic cardiovascular regulation impose certain qualifications on the application or extrapolation of the results to predict integrated barostatic control behavior under "normal" physiological conditions.

One factor is that the results of a majority of these previous studies were compromised by the use of an acute, anesthetized animal preparation, rather than an intact, chronically-instrumented and unanesthetized animal preparation. It is generally recognized that the use of anesthetic agents, required in the acute animal preparation, and the acute surgical procedure itself may inhibit or alter the normal function of homeostatic mechanisms in the cardiovascular system.[41] Consequently, it is unclear whether or not the cardiovascular frequency response characteristics obtained for acute, anesthetized animals are valid for the normal awake animal. As a result, an unanesthetized, chronically-instrumented preparation was used in the present study. An added advantage of the chronically-instrumented preparation is that the quality and stability of pressure and flow signals is generally better than that obtained for acute instrumentation, especially in dynamic stress environments.

A second limitation of previous work is that most often the experiments were not designed to delineate neural and nonneural

contributions to the measured responses. This delineation becomes essential when a total circulatory stimulus such as whole body acceleration is applied to the cardiovascular system, such that resultant pressure/flow changes will be distributed throughout the total circulatory network, and the measured responses will reflect the interactive effect of the disturbance, the passive properties of the vascular components, and reflex barostatic activity. In the present study the animal subjects were studied in a normal neurally reflexive state and in a state of pharmacologically-induced autonomic blockade, where action of the central barostatic regulatory mechanisms was inhibited. Using this approach, results in the latter case serve as a "baseline" for comparison with the normal overall responses, thus enabling the delineation of the neural and nonneural response components. In addition, each animal serves as his own "control" for this comparison.

The third shortcoming of previous efforts to study barostatic cardiovascular control from the standpoint of Systems Analysis is that the frequency response characteristics of only isolated facets of the regulatory network, in response to very localized acutely-applied stimuli, were investigated. Since the interactive relationship of the individual regulatory mechanisms is not simply additive, it would be desirable to study cardiovascular regulation from the standpoint of integrated control, where the natural interplay of individual barostatic control mechanisms is preserved and nonlinear responses are present only to the extent that they occur in the normal interactive system. In order to study the dynamics of integrated barostatic cardiovascular control an appropriate total-circulatory stimulus or "forcing function"

must be chosen, preferably one that is similar to that most normally seen by the cardiovascular system. As noted in the introductory chapter, transient acceleratory loadings associated with normal daily activity, exercise conditions or severe occupational environments are among the most common noninvasive stimuli seen by the cardiovascular system. Consequently, low frequency whole body acceleration was used in the present work as a suitable noninvasive forcing function for the investigation of integrated reflex cardiovascular regulation.

Finally, a systematic study of cardiovascular performance during exposure to low frequency whole body acceleration using a chronically-instrumented, unanesthetized animal preparation is a unique contribution to the body of knowledge on cardiovascular control in that it provides explicit information about normal integrated barostatic regulation under the influence of a natural noninvasively-applied stimulus.

CHAPTER IV

EXPERIMENTAL DESIGN AND PROTOCOL

Presented in this section are details of the experimental design and procedures, including the chronically instrumented animal preparation, the autonomic blockade procedure, the centrifuge facility and the acceleration protocol.

Chronically Instrumented Animal Preparation

Adult male and female mongrel dogs of 17-19 kg body weight were used as animal subjects in this study. The principles of laboratory care outlined by the National Society for Medical Research were rigorously observed in all phases of this work.

The surgical procedures for the chronically instrumented preparation were performed aseptically in the animal care facilities of the Wenner-Gren Research Laboratory at the University of Kentucky. Thoracic implantations were made through an incision in the left fourth intercostal space, with the animal under sodium pentothal anesthesia and on artificial positive pressure breathing. After disection from its attachments, the base of the ascending aorta was reinforced with a nylon curtain material to stimulate fibrotic growth and thereby prolong survival and enhance fixation of an electromagnetic flow transducer (Zepeda Instruments) to the vessel wall. A left ventricular pressure transducer (Konigsberg Instruments, P-21) was placed through the apex of the heart, to project 1 cm into the left ventricular chamber. This

distance was too short for the transducer to swing freely and impact the ventricular wall, but long enough to avoid trapping in the contracting ventricular muscle which could result in artifact due to lateral compression of the transducer diaphragm. In addition, a cannula was placed in the right atrium for the administration of drugs. The cannula and transducer leads were exteriorized into a specially designed subcutaneous nylon velour pouch.[42] This allowed access to the leads whenever desired without the need for anesthesia or dissection. The left thoracic incision was closed in layers, and the animal allowed to recover. Each animal was allowed at least four weeks of postoperative recovery before studies were instituted. Postoperative management included antibiotic coverage and particular attention to nutritional, hematologic and urinary factors in addition to overall clinical evaluation. Studies were not done unless and until these factors were stable at values indicating a satisfactory state of health.

On the day of the experiment, the animal was tranquilized with an intramuscular injection of Innovar Vet at .075 cc/kg. Peizoelectric manometer-tipped catheters (Millar PC 350, 5 French) were placed, under local anesthetic, in the right and left ventricles via small branches of a main femoral vein and artery, respectively. One Millar gauge was used to calibrate the implanted Konigsberg gauge and then retracted into the aorta, just outside the aortic valve, to measure arterial pressure. The animal was maintained in a lightly tranquilized state for the duration of the experiment with serial injections of Innovar (0.5 cc/hr) administered through the right atrial cannula.

The measured physiological variables included aortic pressure and flow, left and right ventricular pressure, and heart rate (derived from

left ventricular pressure). It was determined that these constituted the minimum required variables for the evaluation of systemic cardiovascular performance during whole body acceleration stress. The use of a minimal amount of implanted instrumentation (i.e., only that deemed essential to the experiment) is generally recognized to result in a healthier, more viable animal preparation.[41]

Procedure For Autonomic Blockade

In order to delineate the neural and nonneural components of the measured cardiovascular responses to acceleration, a pharmacologically-induced total autonomic blockade was used to inhibit adrenergic and cholinergic efferent activity (Figure 1), thus removing normal reflex barostatic action. This approach was chosen because the use of pharmacological blocking agents has several advantages over other techniques in that: 1) It is a standard procedure with many of its limitations well documented, 2) The effects of these agents are distributed throughout the system and do not have the uncertainty associated with attempts at total denervation, and 3) The use of these agents allows for repeated blocked and nonblocked studies on the same animal without compromising the integrity of the preparation.

Specifically, the total autonomic blockade for the present study consisted of the alpha adrenergic blocker phenoxybenzamine (Dibenzyline) at 20 to 30 mg/kg administered over an hour, followed by beta blockade with propranolol (Inderal) at 1 to 4 mg/kg over approximately ten minutes, followed by cholinergic blockade with atropine (Atropine Sulphate) at 0.1 to 0.4 mg/kg over approximately five minutes. The efficacy of the blockade was tested and verified by a comparison of systemic responses to specific agonists given prior to blockade,

following blockade and then again at the conclusion of the blocked acceleration sequence. These consisted of a 50 μg/kg bolus of phenylephrine (Neosynephrine) to test the apha blockade and a 0.5 μg/kg bolus of isoproterenol (Isuprel) to test the beta blockade. If heart rate showed evidence of parasympathetic activity (i.e., a decrease) the atropine dosage was supplemented. This blockade and test procedure is discussed in greater detail elsewhere.[43,44]

Centrifuge Facility

Low frequency acceleration loadings were produced by a 50 ft. (15.24 m) diameter centrifuge shown in Figure 2. This system was used to produce sinusoidal acceleration below 1.0 Hz at $\pm$ 2G_z (1 G = 9.806 m/sec^2). Mounted to the large arm of the centrifuge (Figure 2-a) is a platform (Figure 2-b) capable of rotation speeds from 0.005 to 11.5 rad/sec. The animal subject was restrained horizontally on this platform so that its center or rotation was approximately at heart level. With the large centrifuge arm rotating at an appropriate speed to produce the desired radial peak acceleration, an initiation of the platform rotation produces sinusoidal G_z (spinal axis) acceleration loadings. This configuration also produces sinusoidal G_y (lateral) acceleration 90° out of phase with that of G_z, and a +1 G_x acceleration vector due to Earth gravity. The exact time representations of the G_z and G_y acceleration loadings are given by:[45]

$$G_z = [-\omega_R{}^2 R \cos(\omega_r t) - (\omega_R + \omega_r)^2 r]e_r$$

and

$$G_y = [-\omega_R{}^2 R \sin(\omega_r t)]e_p$$

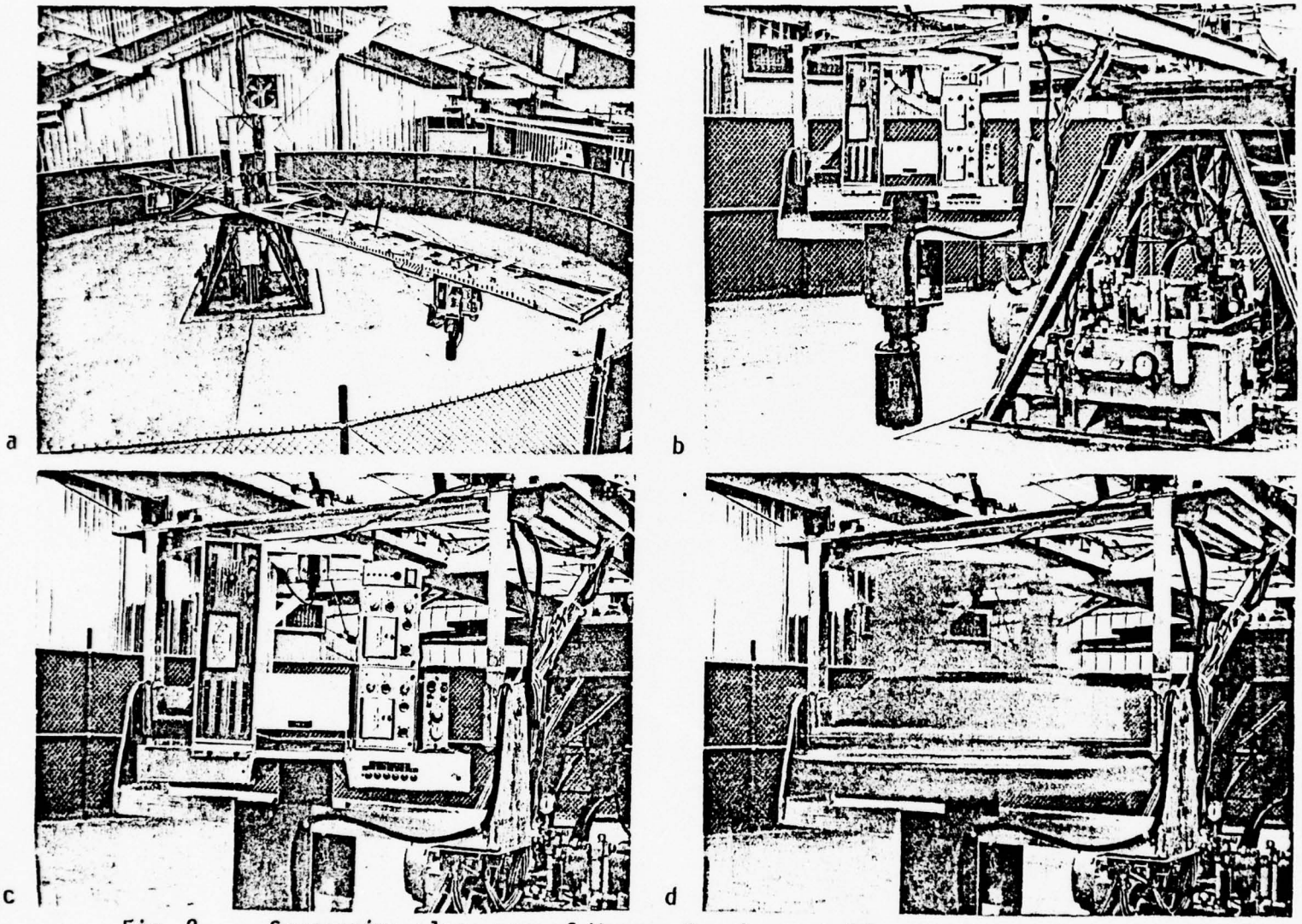


Fig. 2. Successive close-ups of Wenner-Gren's centrifuge modification:
a. Rotating platform mounted on arm of conventional centrifuge
b. Close-up of modification detailing rotating platform with associated drive train
c. Close-up of modification detailing animal restraint with associated instrumentation
d. Time exposure of rotating platform

where

R = the radial distance from the center of rotation of the large centrifuge arm to the center of rotation of the platform,

r = the radial distance from the center of rotation of the platform to an arbitrary point along the spinal axis of the animal,

ω_R = the rotational speed of the large centrifuge arm,

ω_r = the rotational speed of the platform (determines the acceleration frequency),

e_r, e_p = unit vectors.

It should be noted that the G_z component of acceleration contains two terms. The first is the desired spinal axis sinusoid of constant amplitude. The second is a "bias" term representing a dc offset of this sinusoid due to the interactive effect of the rotation rates ω_r and ω_R at various distances r along the spinal axis, away from the platform's center of rotation (r = 0). This bias term can be minimized (or negated) by a proper choice of ω_R and ω_r, with the two being of opposite sign. In the present study R = 6.10 m and ω_R = 1.8 rad/sec, which yielded the desired 2 G_z sinusoid with less than a 0.006 G/cm bais along the animal's spinal axis for acceleration frequencies from 0.005 to 0.25 Hz.

While cardiovascular responses to G_y and G_x sustained acceleration have been shown to be relatively small when compared to those of the G_z direction,[1] their potential influence cannot be totally disregarded when interpreting data from these experiments.

All physiological signals from the animal, and G_z acceleration were conditioned and preamplified by electronics contained on the rotating platform (Figure 2-c), and then transmitted through two sets of slip rings (platform and centrifuge axes) and a long line interface to a remote location where they were monitored and recorded.

Acceleration Protocal

An acceleration amplitude of $\pm$ 2 G_z was chosen for this study for a number of reasons. It was felt that this acceleration level would represent a stress somewhat greater than that seen by the animal during normal physical activity, but less than that which might produce total circulatory collapse. The latter possibility was of particular concern during the blockaded runs, where the animal's compensatory mechanisms were purposely compromised. In addition, it was estimated that this acceleration level would generate intravascular pressure disturbances in the range of $\pm$ 10-20 mm Hg, similar to the invasively-applied pressure stimulus used in previous studies.

On the day of experiment, after placement of the acute instumentation, the animal was placed in the restraint couch and mounted on the rotating platform (Figure 2-c). The instrumentation leads were then connected and tested, and all signals were calibrated, thus readying the animal for the test series.

All variables were allowed to stablize for a pre-acceleration control period. The test series then consisted of $\pm$ G_z sinusoidal acceleration at discrete frequencies in the range form 0.005 to 0.25 Hz. The frequencies were run sequentially (low-tO-high in most animals) without stopping, allowing from 3.0 - 4.0 min at the low frequencies and 1.0 - 2.0 min at the highest. It was felt that this continuous

frequency "sweep" would minimize startling responses associated with centrifuge start up and shut down, thus enhancing the stability of responses at each frequency. A number of animals were run using random sequencing of the frequencies, and both low-to-high and high-to-low protocols to determine the influence of these factors on the overall responses. At the conclusion of the frequency sweep the animal was allowed a suitable recovery period, during which all variables could return to pre-acceleration control levels. Next the animals were tested to determine their pre-blockade response to the appropriate adrenergic agonists (see second section this chapter), after which the total blockade was implemented and a second post-blockade, pre-acceleration test made. The same control-test-recovery sequence used in the nonblocked run was then repeated. Finally, another test was made to verify survival of the total blockade.

Following the experimental run, data analysis proceeded as outlined in the next chapter.

CHAPTER V

DATA ANALYSIS

During each experimental session, a continuous on-line magnetic tape record (Ampex FR-3020, 14 channel recorder) and a strip chart record (Beckman Type-RM Dynograph, 7 channel recorder) was made of the following variables: spinal axis acceleration (ACC), heart rate (HR), aortic pressure (AP) and flow (AF), right ventricular pressure (RVP), and left ventricular pressure (LVP). The HR variable was generated by a calibrated cardiotachometer (Beckman Type 9857B) triggered from the phasic LVP signal. The strip chart data was reviewed, off-line, to determine exact acceleration frequencies, and inclusive tape counts and record (time) lengths for each edited "window" of data to be digitally sampled and Fourier analyzed.

The sampling and analysis were carried out on a Digital Equipment Corporation (DEC) PDP-11/10 minicomputer system, with the aid of the DEC LAB APPLICATIONS-II, V-3 library package and a number of user-written BASIC applications programs.

Fourier analysis techniques were applied to these data, rather than a "by hand" quantitative method for several reasons: First, Fourier analysis is a standard analytical approach to the quantitative description and evaluation of system dynamics where the time-dependent response of particular system variables (e.g., AP, DRVP, AF and HR) to an externally-applied sinusoidal forcing function (e.g., ACC) can be experimentally measured. Secondly, variations in results due to the

variability or biases of human interpretation are eliminated by the strict application of a consistent analytical method to the data. Finally, in addition to information about the amplitude of output responses, Fourier analysis provides information about the time relationship (phase lead or lag) of the responses of output variables with respect to the input function and each other; information which is not easily obtained with hand analysis, but which is necessary for modeling of system responses.

Digital Sampling, Scaling and Filtering of Analog Signals

As a general rule-of-thumb, a digital sampling frequency is chosen to be greater than, or equal to four times the highest frequency content of the analog signal being sampled.[46] Since phasic aortic flow and left ventricular pressure signals typically have frequency content of up to 30 - 40 Hz[40], a digital sampling frequency of 161 Hz (6.2 msec interval) was used for all variables in the present work. This insured accurate digital reproduction of the analog response signals, as shown in Figure 3. At this point, however, the data was not in a format suitable for direct frequency analysis.

Due to core memory limitations of the PDP-11/10, and the specific Fourier analysis algorithm employed in the LAB APPLICATIONS software package, the 1.0 to 3.0 minute time records had to be filtered and compressed into a form where each was represented by 512, 1024 or 2048 points before the frequency analysis could be carried out. All data were digitally filtered in the time domain with a low pass 0.32 Hz, 40 dB/decade Bartlett filter[47] to remove the phasic (beat-by-beat) frequency content of each time record, while preserving the oscillatory components related to the acceleration forcing function. The normalized

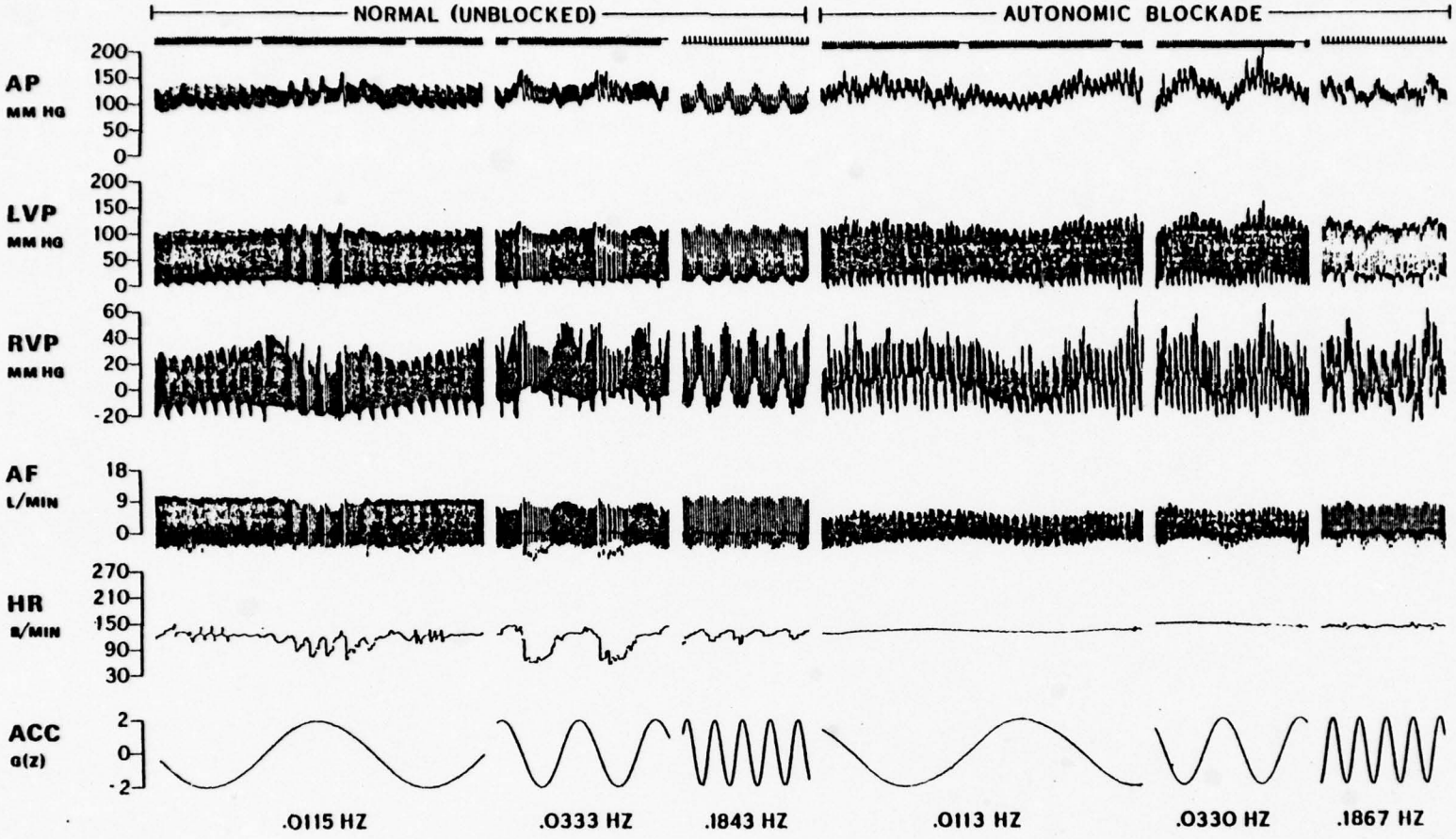


Fig. 3. Example of phasic cardiovascular data: The response of one animal in both a nonblocked and autonomically-blocked state at three acceleration frequencies, with one secend event markers shown above the AP traces.

amplitude attenuation of this filter was of the form:

$$A = [(1/\pi f)\ \ SIN(\pi f)]^2$$

where A is the amplitude of the sinusoidal output of the filter for an input sinusoid of unity amplitude and frequency f (Hz). A linear (frequency dependent) phase shift corresponding to a time shift of 1.0 sec is associated with this filter. The phasic analog data shown in Figure 3 is presented in its digitally-filtered form in Figure 4. The purpose of filtering the sampled data was to avoid the phenomen of spectral "aliasing"[46] in the compressed data, and hence in the Fourier analyzed results.

Each set of filtered time records (a "set" being the AP, DRVP, AF, HR, and ACC time record at a given test frequency) was next reduced to a compressed 512, 1024, or 2048 point representation by extracting and saving every n^{th} point ($8 \leq n \leq 15$). The exact choice of n for each test depended upon the test frequency and time length of data in the test record, and was made so that the resulting compressed time records represented an integral number of acceleration cycles as closely as possible. "Leakage" effects[46] which can lead to inaccuracy in the Fourier analyzed data are significantly reduced the more closely this criterium is met. The time records were therefore edited so that the compressed data represents an integral number of acceleration cycles to within $\pm$ 15% of a cycle, thereby keeping leakage errors in the amplitude information of the first Fourier component to less than 4% in the analyzed data.

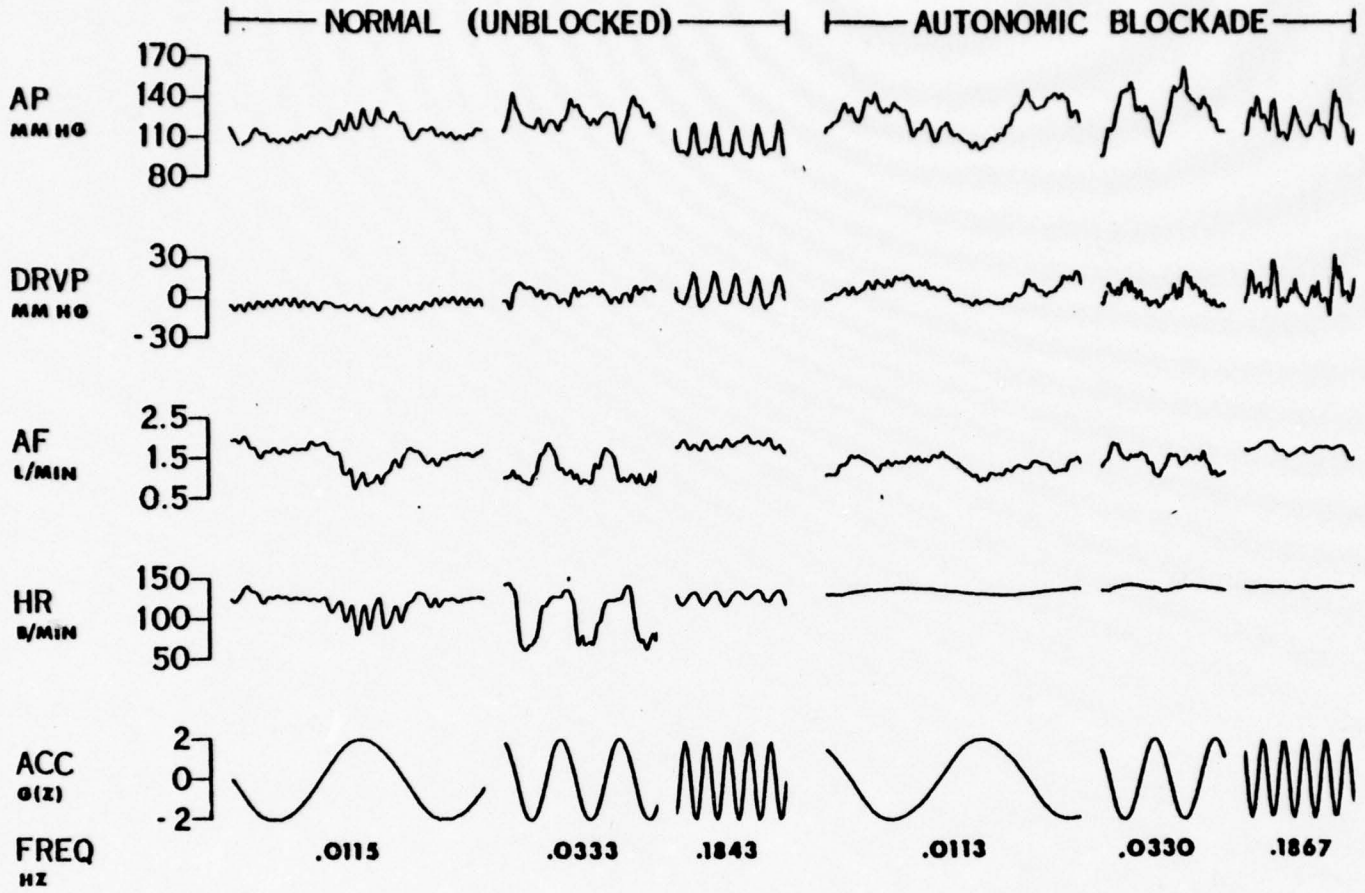


Fig. 4. Example of filtered cardiovascular data: The digitally-filtered representation of the phasic response data from the preceding Figure, for one animal in both a nonblocked and autonomically-blocked state at three acceleration frequencies.

Fourier Analysis of Filtered, Compressed Data

After filtering and compression the paired input (ACC) and output (AP, DRVP, AF, and HR) waveforms were Fourier analyzed using the SPARTA program from the LAB APPLICATIONS library. Two additional calculated output variables, effective systemic resistance ER = (AP-DRVP)/AF and stroke flow SF = AF/HR were also frequency analyzed. The SPARTA program utilizes a Radix-2 in-place algorithm[47] to compute a discrete Fourier transform of the form:

$$F_r = \sum_{k=0}^{N-1} X_k \exp(-2\, rkj/N)$$

$$= a_r + jb_r,\ r = 0,1,\ldots.N-1$$

where

F_r = the r^{th} coefficient of the Fourier transform, for which a_r and b_r are the real and imaginary components.

X_k = the k^{th} point of the complex time series which consists of N samples (N = 512, 1024, or 2048).

The real and imaginary coefficients are combined to yield the magnitude/phase representation of the Fourier spectrum:

$$A_r = (a_r^2 + b_r^2)^{\frac{1}{2}}$$

$$\phi_r = \arctan (b_r/a_r)$$

where

A_r = the amplitude of the r^{th} Fourier component of the time record X(t).

ϕ_r = the corresponding phase of the r^{th} Fourier component.

The frequency of the r^{th} component is equal to $r\Delta f$, where Δf is the frequency resolution of the Fourier spectrum; which is $1/N\Delta t$, N being

the number of points in the compressed time record and Δt the time interval between samples. For the compressed data $0.0496 \leq \Delta f \leq 0.093$ msec, so that the frequency resolution in the computed spectra was $0.005 \leq \Delta f \leq 0.0394$ Hz. The maximum frequency represented in a given Fourier spectrum was $f_{max} = 1/(2\Delta t)$, which for this work yielded $5.376 \leq f_{max} \leq 10.08$ Hz. Thus f_{max} was well into the effective filtering range of the low-pass filter applied to the original sampled data. As a result, aliasing should not have occurred in the computed spectra.

The mean (nonoscillatory) response and amplitude/phase values of the first several harmonics (of the input acceleration frequency) were saved from the computed spectrum of each output variable. In specific cases, where predictable inaccuracies due to spectrum "leakage" or the digital filtering occurred in the data, suitable correction factors were applied. An example of the Fourier analyzed power spectra for the HR response of one subject to 0.008 - 0.65 Hz, $\pm$ 2G sinusoidal acceleration is shown in Figure 5, which is a composite plot of the individual amplitude spectrum for each distrete input frequency. While second and third harmonics of the input acceleration frequency can be seen, predominance of the first harmonic in the response is apparent.

Grouping of Data, Statistical Treatment

While the presentation of data for individual animals is appropriate to emphasize specific aspects of acceleration-induced cardiovascular responses, the presentation of group data is desireable in so far as it serves to demonstrate the similarity of responses of all animals, facilitate the comparison of nonblocked and autonomically-blocked responses, and the identification of frequency-dependent trends in the responses. Due principally to practical hardware limitations associated

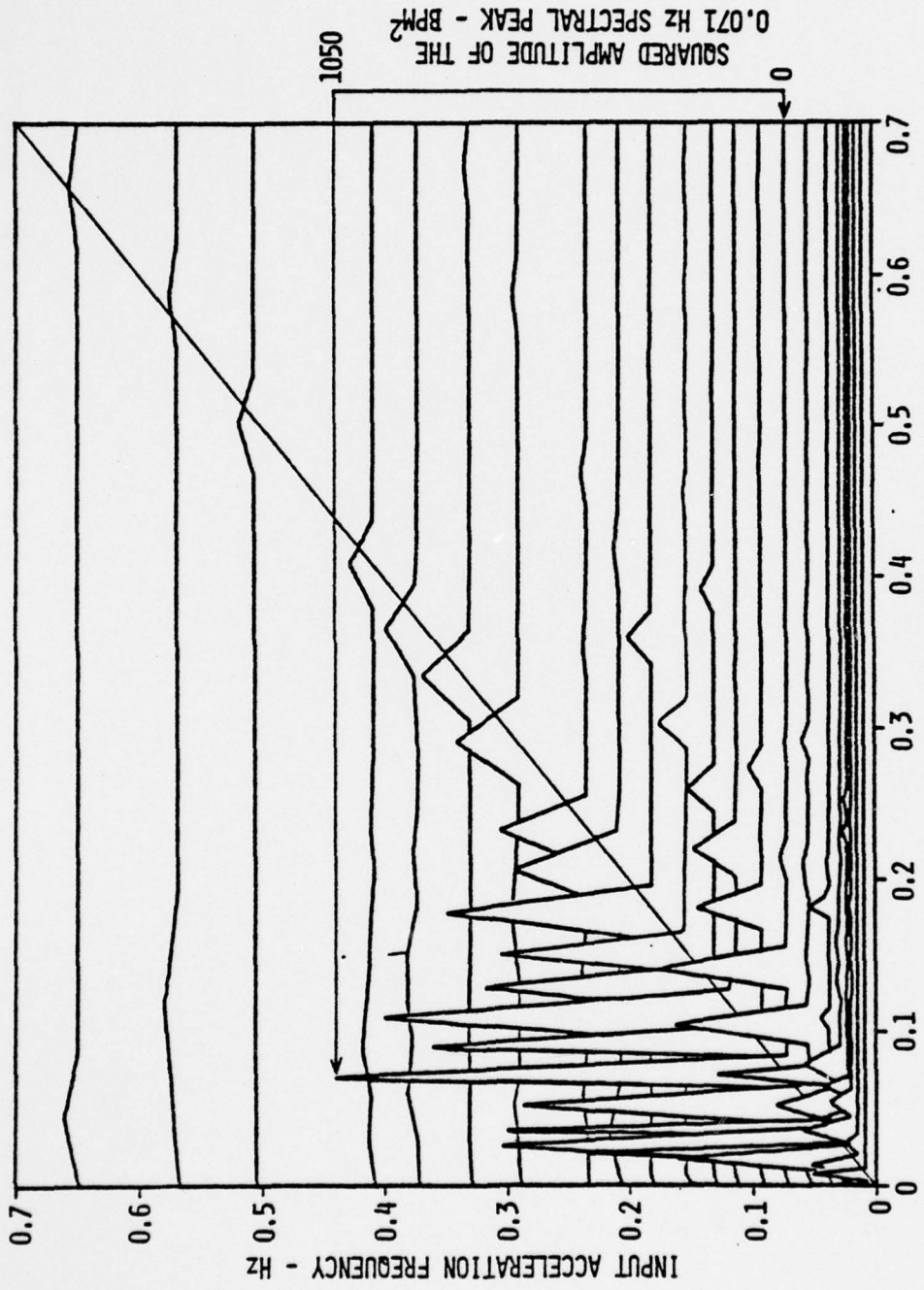


Fig. 5. Orthogonal (3-dimensional) representation of the squared amplitude of heart rate response versus spectral frequency, as a function of input acceleration frequency, for one nonblocked animal during exposure to 0.008 - 0.650 Hz, ± 2 g(z) sinusoidal acceleration.

with the operation of the centrifuge facility, acceleration test frequencies were not matched exactly for individual subjects during the nonblocked and blocked runs, nor from one animal to the next. Consequently, for the presentation of group responses, the data are grouped into nine frequency ranges and averaged. The frequency ranges are given in Table 1, and have been selected so that each animal is represented within a given range for both the nonblocked and blocked runs. In cases where an individual subject was run at more than one test frequency within a frequency range, the subject's data were averaged. The data for all animals were then averaged and statistically compared, by frequency range, for both the nonblocked and blocked states using an analysis of variance test called Treatments-By-Subjects Design.[48]

This statistical analysis is a variation of Completely Randomized Design, except for the use of only one group of subjects, with each receiving all the treatments (frequency ranges, and blocked and nonblocked states). This analysis of the data is based on the subjects' performances while under the influence of each of the treatments. Completely Randomized Design was also used to check for carry-over effects from one treatment to the next, which is not tested for with the Treatments-By-Subjects Design. After the analysis of variance is satisfied, a t-Test for the Difference Among Several Means derived from Treatments-By-Subjects Design is used to determine which means differ from each other. In order not to violate the Probability Theory all treatments are tested, as seen in Table 1. Table 1 is a comparison of group means of various cardiovascular response variables by frequency

Table 1.

STATISTICAL COMPARISON OF UNBLOCKED VERSUS AUTONOMICALLY BLOCKED GROUP MEANS of variables for nine frequency ranges; using a t-Test for Difference Among Several Means, with two-tailed alpha levels (derived from Treatment-By-Subjects Design, repeated measures on one factor).+
The level of significance is as indicated, with blanks denoting a P>.05 (not significant).

		.005 to .012 Hz	.012 to .021 Hz	.021 to .032 Hz	.032 to .052 Hz	.052 to .077 Hz	.077 to .110 Hz	.110 to .150 Hz	.150 to .200 Hz	.200 to .250 Hz
AP	mean amplitude	.01	.01	.001	.01	.01				
	phase	.05	.01	.05	.05	.05	.05	.05	.05	.05
DRVP	mean amplitude	.05								
	phase	.05								
ER	mean amplitude	.001	.01	.001	.001	.01	.01			
	phase			.05						
AF	mean amplitude	.01		.05	.05		.05	.05	.05	.05
	phase	.05	.01	.001 .01	.001 .001	.01 .001	.01 .001	.05 .001	.05	.01
HR	mean amplitude	.05	.05	.001	.001	.001	.001	.001	.001	.01
	phase*									
SF	mean amplitude	.001	.01	.01	.001	.01	.01	.001	.001	.001
	phase	.001	.01	.001	.001	.001	.01	.001	.001	.01

+Refer to text for further description *Autonomically blocked phase values not available

range, in the nonblocked versus blocked states, with levels of significance for the difference between means appropriately indicated.

CHAPTER VI

RESULTS

Experiments were conducted on eight adult, male and female dogs, and the results were considered for presentation. Since a comparison of nonblocked and blocked responses was a principal concern in this study, one subject was dropped from consideration due to loss of blockade during the experiment. Two other animals were dropped, because of malfunctioning pressure or flow instrumentation. The resulting group of five animals (hereafter refered to as the "group") consisted of two females and three males of 18 kg average body weight which were tested from between 4 to 6 weeks postoperatively. For the group, all physiological signals were of good quality and all animals were shown to have maintained blockade during that portion of the experiment. Because of the volume of data obtained, a specific format will be followed in the presentation of essentially all the results.

The graphical and written presentations will both be based primarily on a comparison of the nonblocked and blocked group response of particular cardiovascular variables as a function of acceleration frequency. Due to similarities in the particular responses of individual animals, it was felt that the data should be presented in group form, rather than for individual animals, and that the presentation of composite data would enhance the strength of observations about and discussion of the results. At the conclusion of the chapter some individual results will be given, however, to

illustrate this point and to demonstrate the influence of random and low-to-high versus high-to-low frequency sequencing. The reader is refered to the preceeding chapter for a description of the procedure used to compute averaged group responses, and the statistical treatments of the data. In addition, it should be noted that the data have not been normalized with respect to acceleration level (i.e., response value per G) since the acceleration input or forcing function was of a constant 2 G amplitude.

With reference to Figure 4 it can be seen that while the input function (ACC) is sinusoidal, the output responses (AP, DRVP, AF and HR) are definitely nonsinusoidal, implying a nonlinear input/output relationship. In cases where output oscillations are seen, they contain a major component at the same frequency as the input acceleration frequency. Thus the input/out relationship will be presented using a "describing function" technique[49] which is a frequency-response method for handling nonlinear systems. The describing function method of analysis is based on the premise that the input/output relationship of a nonlinear system may be linearly approximated by comparing the amplitude ratio and relative phase of the fundamental (Fourier) component of the output response to an input sinusoid, as long as the system response meets several criteria. The first criteria is that there must be an oscillatory component of the output at the same frequency as the input, with higher harmonics of the output being at integer multiples of the input frequency and of lower amplitude. This condition was met with respect to the present data (Ref. Figure 5). Other frequency content in the data can be disregarded insofar as it is attributable to other inputs and does not occur at or near the

frequency of interest (e.g., the high frequency respiratory artifact in AP and DRVP, Figure 4). Another restriction of the approach is that the system may contain not more than one nonlinearity or, that if it does they can be lumped into a single nonlinear element. In the present study this was an implicit assumption, as noted in the statement of the problem (Ref. Chapter III). A final restriction is that the system nonlinearity must be stationary (i.e., not change with time), and only be a function of the amplitude and frequency of the input function. With each change of input acceleration frequency the experimental output waveforms went through a short transient readjustment and then stabilized (i.e., became stationary). Since the above criteria were met, the experimental data will be presented in describing function form. Consequently, the graphical representation of the response of each variable will generally include the following information for both the nonblocked and blocked tests: 1) The mean value of the response for control and recovery periods (pre- and post-acceleration respectively) and for the acceleration series, and 2) The amplitude and relative phase of the first (fundamental) Fourier component of the response, as a function of acceleration frequency (output lagging input denoted by positive phase angles).

Since sinusoidal acceleration was the primary stimulus applied to the cardiovascular system, the response of each of the measured variables (AP, DRVP, AF and HR) and calculated variables (ER and SF) will be examined from the standpoint of their relationship to acceleration.

Individual Cardiovascular Variables (Group Response Relative to Input Acceleration)

The response of the controlled variable, aortic pressure (AP), is shown in Figure 6. After the initiation of the acceleration run there is an overall stress response, indicitated by a 10 - 30 mm Hg increase in AP mean. This increased pressure is maintained throughout the entire test series at an almost constant level, and remains into the recovery period. Except for the pre-acceleration control period, there was no significant difference between blocked and nonblocked AP means. On the other hand, blocked AP amplitude has a significant frequency-dependent response, with a peak of 18 mm Hg at 0.04 Hz, and a tendency toward reduced oscillations at higher frequencies. Viewing blocked AP amplitude as the passive acceleration-induced "open loop" input to the baroreceptors, and comparing these oscillations with the nonblocked AP amplitude response, it can be seen that reflex barostatic mechanisms are able to achieve a significant degree ($P>.01$) of reflex adjustment for frequencies up to about 0.08 Hz. Above this frequency there was no significant difference between nonblock and blocked AP amplitude, indicating a lack of effective regulatory response. These features of the AP response are better illustrated in Figure 7, which shows the relative nonblocked/blocked response. Of special interest in Figure 7 is the relative AP amplitude which is equal to the (nonblocked-blocked)/blocked AP amplitudes from Figure 6. With a value of 1.0 denoting no compensatory regulation, relative AP amplitude indicates a 30 - 35% reflex adjustment of the passive (i.e., blocked) acceleration-induced pressure disturbances up to 0.07 Hz. Blocked AP phase (Figure 6) exhibits a

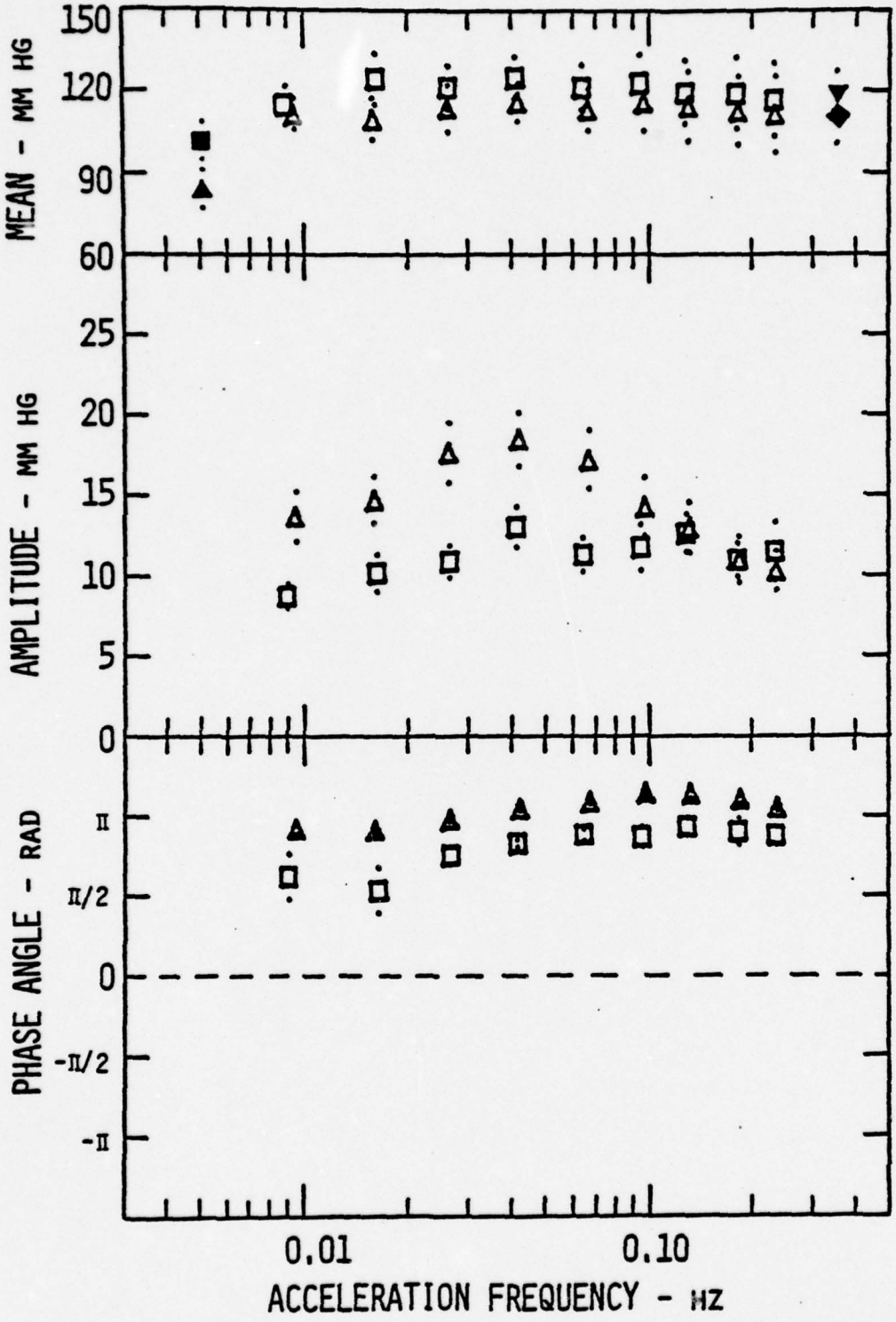


Fig. 6. AORTIC PRESSURE: mean, amplitude and phase of the first Fourier component with respect to acceleration (□ unblocked, △ autonomic blockade, ■▲ control and ◆▼ recovery values; ⁚ ± SEM) for a group of 5 animals.

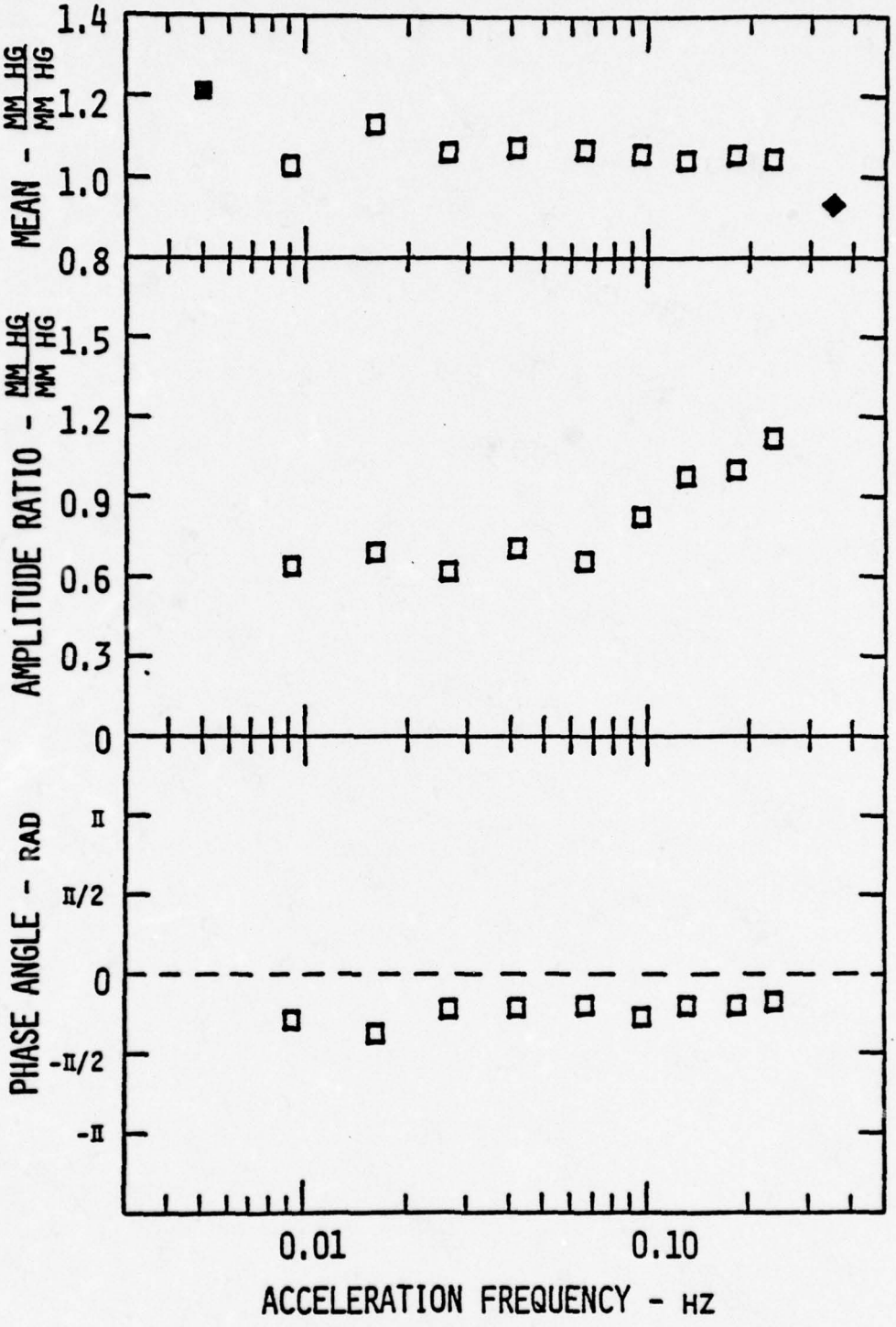


Fig. 7. RELATIVE UNBLOCKED/BLOCKED AORTIC PRESSURE RESPONSE: mean ratio, amplitude ratio and relative phase of the first Fourier components as a function of acceleration frequency, for a group of 5 animals (■ control and ◆ recovery values).

definite frequency-dependent trend, but essentially lags acceleration by 180°, thus supporting the contention that the oscillatory blocked AP response represents a passively-produced (i.e., "hydraulic") pressure disturbance within the cardiovascular system. Nonblocked AP phase was similar, but shifted by approximately 30 - 40°.

In contrast to AP, the response of diastolic right ventricular pressure (DRVP, which is roughly equivalent to central venous pressure) is essentially identical for both blocked and nonblocked cases, as Figure 8 shows. During the acceleration series there is a slight elevation (3 - 5 mm Hg) in DRVP mean from the control/recovery levels, which is probably indicative of an overall systemic pressor response as was seen in AP mean. The response of DRVP amplitude ranges from 5 to 12 mm Hg, with an apparent (although not significant) trend toward greater oscillatory amplitudes at higher frequencies. Finally, there is a constant 180° lag of DRVP phase with respect to acceleration. These DRVP amplitude and phase data indicate that for the frequency range from 0.008 to 0.25 Hz, the venous system essentially responds to acceleration as a passive element in the circulatory network (i.e., is not a controlled variable). This is not to say, however, that the mean level of central venous pressure is not controlled (i.e., DRVP mean response), nor that venous pressure oscillations are not sensed and do not provide efferent information to the barostatic regulatory mechanisms.

Since the AP data (Figures 6 and 7) indicate some level of effective barostatic regulation, it is important to determine the participation of vascular and cardiac mechanisms in these responses. The first of these mechanisms, effective systemic resistance (ER),

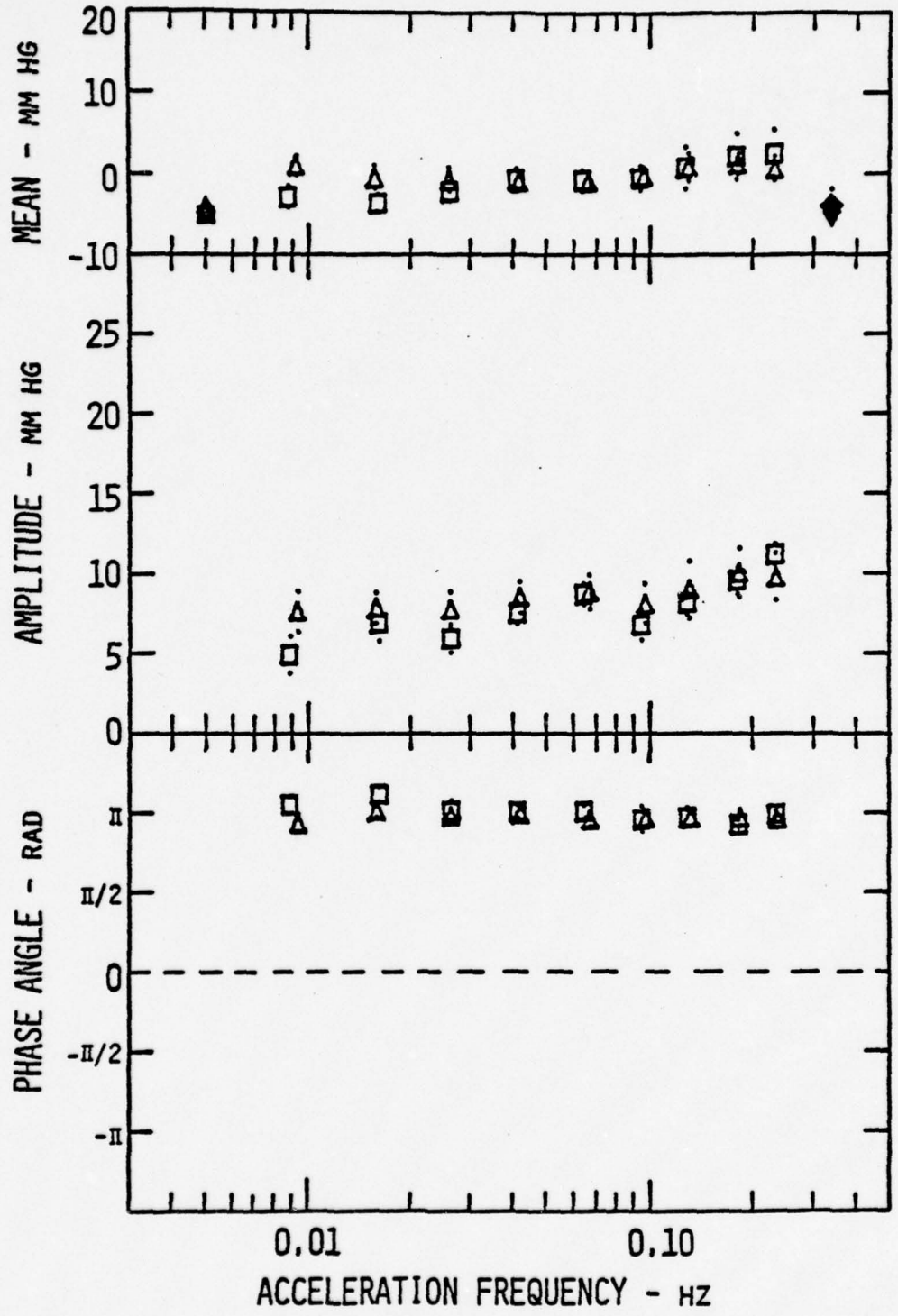


Fig. 8. DIASTOLIC RIGHT VENTRICULAR PRESSURE: mean, amplitude and phase of the first Fourier component with respect to acceleration (□ unblocked, △ autonomic blockade, ■ ▲ control and ◆ ▼ recovery values, ⁚ ± SEM) for a group of 5 animals.

is shown in Figure 9. As noted in the previous chapter, ER is a calculated variable defined as (AP-DRVP)/AF, where AF is aortic flow. Consequently, while ER is not a rigorous measure of resistance on the peripheral vascular level, it does represent an index of the overall or composite level of systemic vascular (resistance) activity. The apparent pressor reflex noted in the rise of AP mean and DRVP during acceleration is also seen in the ER mean response for frequencies up to 0.04 Hz. At the onset of the acceleration run, ER mean goes from a control value of 40 - 50 mm Hg/(L/min) to approximately 65 mm Hg/(L/min) for both the blocked and nonblocked cases. The nonblocked and blocked values of ER mean are not significantly different during either the acceleration series or in the recovery period. Both are essentially constant [(65 - 70 mm Hg/(L/min)] up to 0.04 Hz, with a decreasing trend at higher frequencies. Nonblocked ER amplitude and phase are highly frequency-dependent. The amplitude increases from about 8 mm Hg/(L/min) at 0.008 Hz to a maximum resonant peak of approximately 12 mm Hg/(L/min), followed by a decrease to a value around 4 mm Hg/(L/min) above 0.13 Hz. Nonblocked ER phase increases with acceleration frequency, from 0° at 0.008 Hz to about 150° at 0.065 Hz, remaining 150-180° out of phase with acceleration above 0.065 Hz. These nonblocked ER amplitude/phase data indicate roughly an underdamped second-order response. The blocked ER amplitude response is, however, essentially invariant with frequency (about 4 mm Hg/(L/min)) from 0.008 to 0.25 Hz, indicating that it may represent a nonreflexive baseline or residual level resulting from nonneural factors (Ref. Chapter II fourth section). Consequently, the difference between the nonblocked and blocked ER amplitude can be

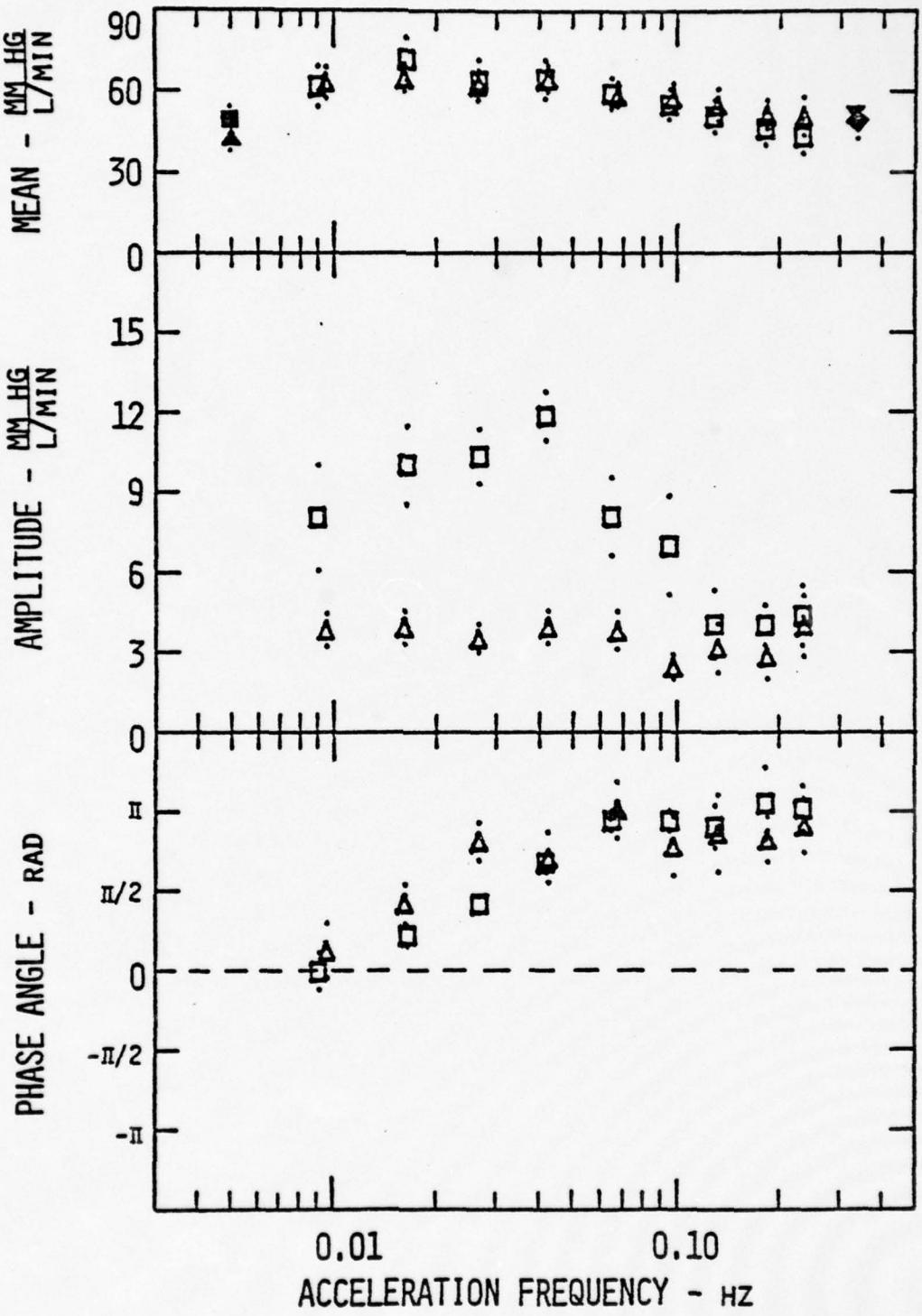


Fig. 9. EFFECTIVE SYSTEMIC RESISTANCE: mean, amplitude and phase of the first Fourier components with respect to acceleration (□ unblocked, △ autonomic blockade, ■▲ control and ◆▼ recovery values, ± SEM) for a group of 5 animals.

taken as the actual active baroreflex-mediated systemic vascular (resistance) response. Furthermore, these ER amplitude data indicate that the pharmacological blockade does in fact inhibit neurally-mediated systemic vascular activity.

The response of aortic flow (AF, equal to cardiac output minus coronary flow), the second determinant of AP, is shown in Figure 10. There was a marginally-significant difference ($P>.05$) between the nonblocked and blocked AF mean response during acceleration. In both the nonblocked and blocked cases AF mean tended to increase with higher acceleration frequencies. This trend in AF mean along with the tendency of ER mean to decrease at higher frequencies (Figure 9) resulted in a more or less constant level of AP mean (Figure 6) throughout the entire frequency range. Control AF mean levels were equal to or slightly greater than the low frequency values (1.8 - 2.2 L/min), while the recovery levels reflected the larger, high frequency values (2.3 - 2.5 L/min). The nonblocked AF amplitude response was approximately twice the blocked response for frequencies above 0.02 Hz, demonstrating the effect of heart rate oscillations (an influence only in the nonblocked tests). At frequencies below 0.02 Hz there was no significant difference between nonblocked and blocked AF amplitude. Both the nonblocked and blocked AF oscillations were about 180° out of phase with acceleration in the low frequency range, and lagged progressively more at higher frequencies. The large difference between nonblocked and blocked AF phase in the range from 0.028 to 0.13 Hz is another consequence of heart rate oscillation, which occurred during the nonblocked tests.

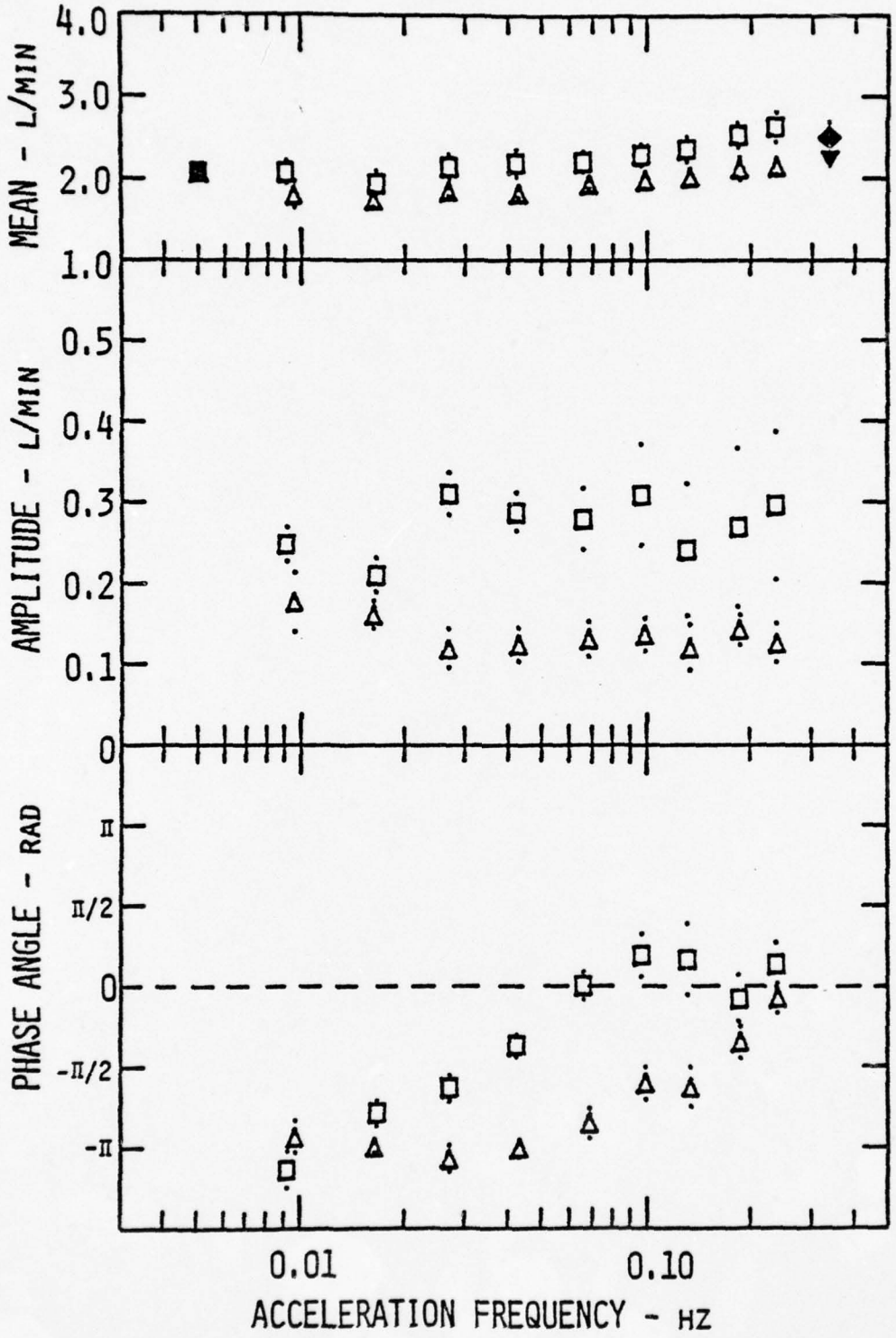


Fig. 10. AORTIC FLOW: mean, amplitude and phase of the first Fourier component with respect to acceleration (□ unblocked, △ autonomic blockade, ■▲ control and ◆▼ recovery values, ⁚ ± SEM) for a group of 5 animals.

Since the behavior of AF responses during acceleration is directly determined by both heart rate and stroke volume changes the response of these variables will be presented next. Heart rate (HR) is shown in Figure 11. The first feature of HR response to note is that the autonomic blockade did effectively inhibit reflex heart rate changes. Blocked HR mean was a constant 135 bpm (beats per minute) throughout the acceleration series, and for the control and recovery periods. Blocked HR amplitude was less than 3.5 bpm, so that blocked HR phase could not be calculated with accuracy, and is therefore not shown. Nonblocked HR mean increased from a resting, control level of 107 bpm to a relatively constant 120 - 125 bpm during the acceleration series, reflecting the overall pressor response seen in previous variables. Nonblocked HR amplitude is highly frequency-dependent, with relatively small oscillations of approximately 8 bpm at 0.008 Hz, increasing to a maximum of 22 bpm at 0.04 - 0.06 Hz, and then decreasing to 9 bpm at 0.23 Hz. At the same time, HR phase leads acceleration by approximately 90° at 0.008 Hz, then increases progressively with frequency through 0° at 0.05 Hz, to a maximum lag of 90° at 0.23 Hz. These HR amplitude/phase data suggest an underdamped second-order type of response.

Stroke flow (SF, approximately equal to left ventricular stroke volume) is shown in Figure 12. Nonblocked SF was consistently 5 - 7 ml/b greater than blocked SF for both the control and recovery periods and during the acceleration series. Noting the reciprocal relationship between HR and SF, this was probably due largely to the higher blocked versus nonblocked HR means shown in Figure 11. Nonblocked and blocked SF mean both increased with frequency, approaching their

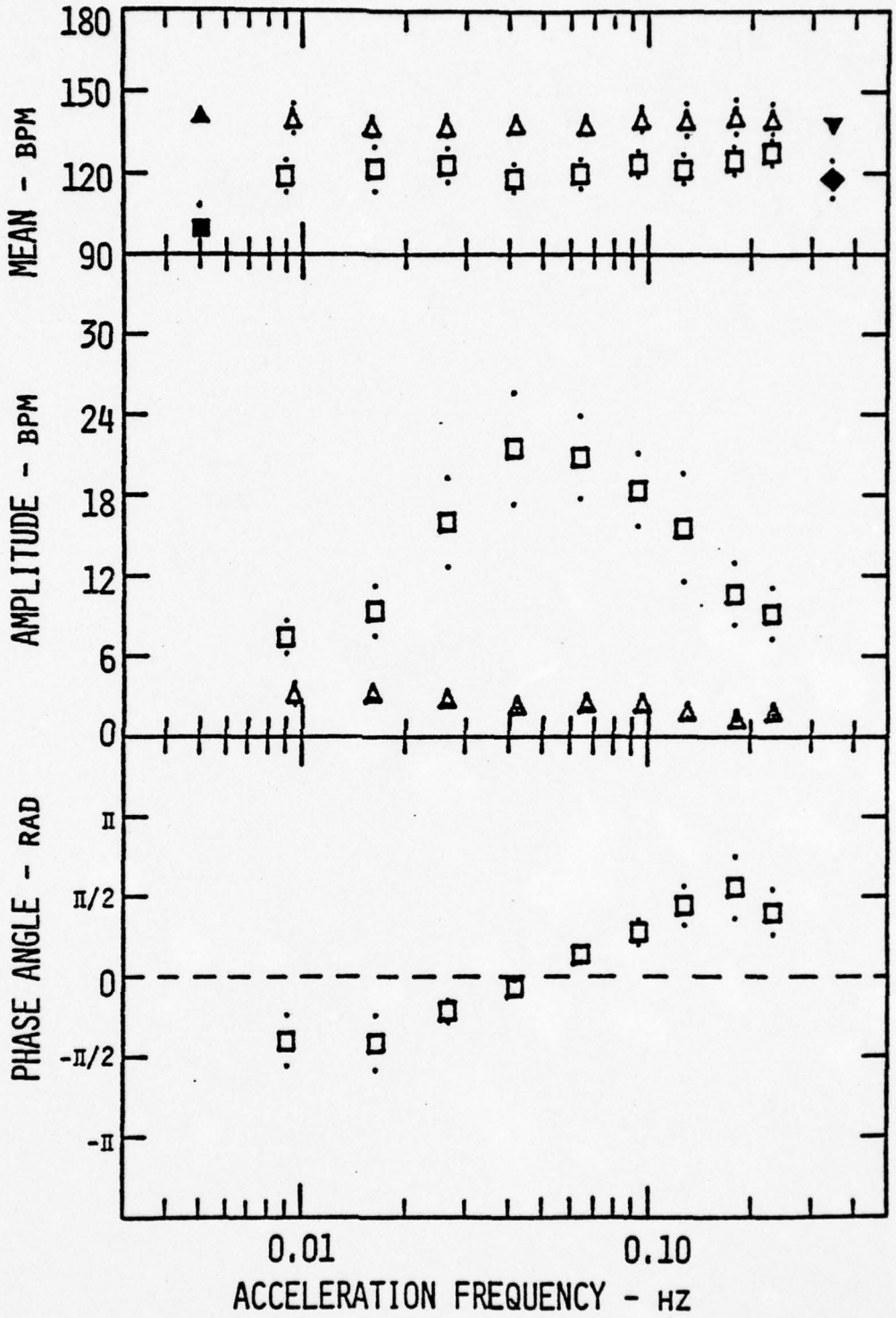


Fig. 11. HEART RATE: mean, amplitude and phase of the first Fourier component with respect to acceleration (□ unblocked, △ autonomic blockade, ■▲ control and ◆▼ recovery values, ⁚ ± SEM) for a group of 5 animals.

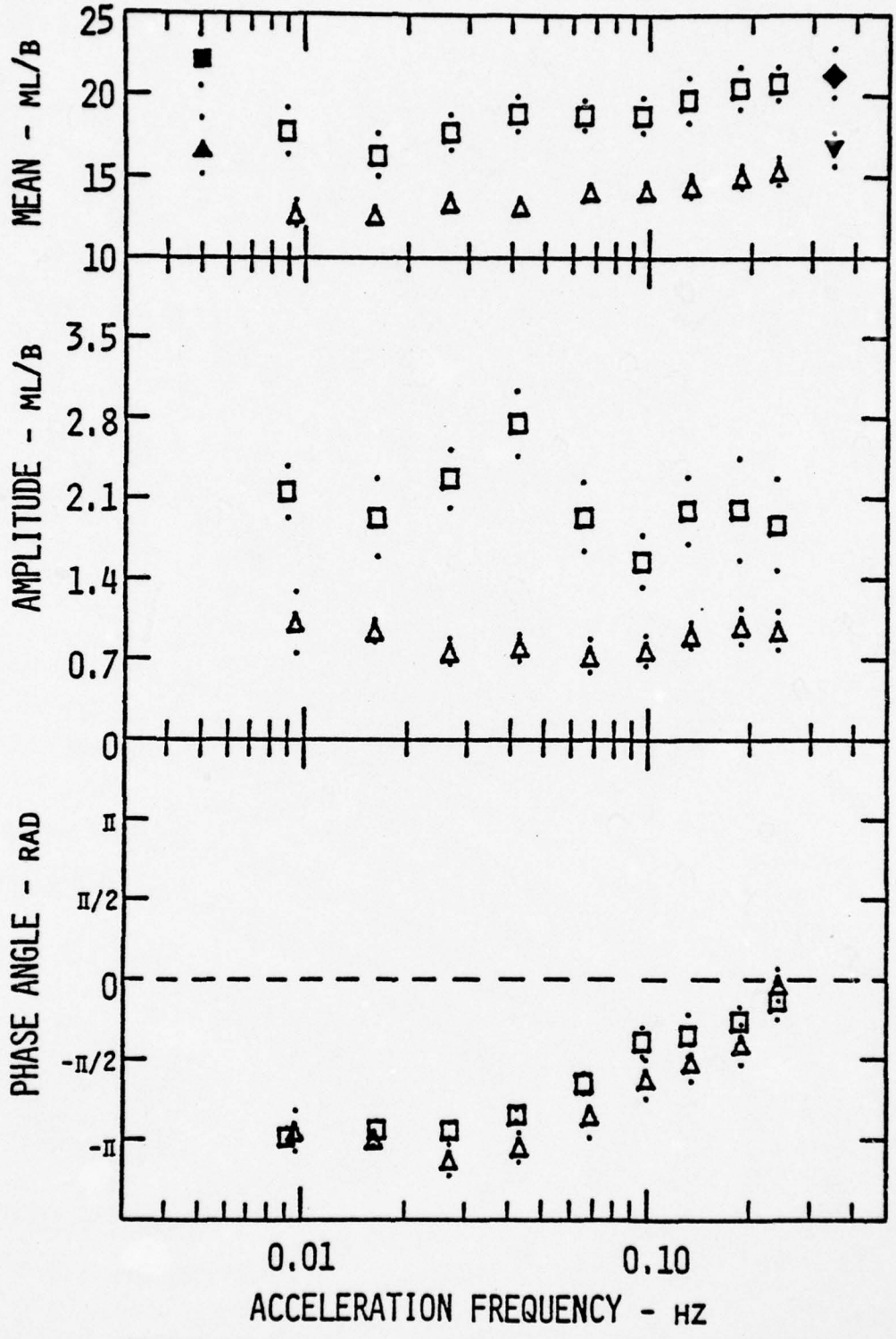


Fig. 12. STROKE FLOW: mean, amplitude and phase of the first Fourier component with respect to acceleration (□ unblocked, △ autonomic blockade, ■▲ control and ◆▼ recovery values, ⁝ ± SEM) for a group of 5 animals.

control/recovery values at the high end of the frequency range. The low frequency decrease of SF mean from control/recovery levels is probably due to increased arterial output impedance (overall pressor response noted in AP mean and ER mean, Figures 9 and 6) while the high frequency recovery of SF mean reflects a relaxation of this pressor activity above 0.05 Hz. Due to the influence of nonblocked HR amplitude and the higher level of nonblocked SF mean, the nonblocked SF amplitude is roughtly 2 - 3 times the response of blocked SF amplitude. Nonblocked SF amplitude shows a slight peaking behavior at about 0.04 Hz, within the frequency range where heart rate has maximal oscillations. On the other hand, blocked SF amplitude is essentially frequency-invariant from 0.008 to 0.23 Hz. There was no significant difference between nonblocked and blocked SF phase. Both were 180^{o} out of phase with acceleration at lower frequencies, then showed a further lagging tendency with increasing frequency.

In summary, it is apparent from the data presented that: 1) With the exception of DRVP, all of the physiological variables examined exhibit significant frequency-dependent behavior, 2) Based upon a comparison of nonblocked and blocked responses, these frequency-dependent characteristics appear to be neurally mediated, especially in the case of ER and HR, and 3) There is an acceleration and frequency dependent variation in overall systemic pressor (venomotor and vasomotor) activity which is evident from the mean response of AP, ER, and AF, that would seem to be nonneural in nature since it appears in both the nonblocked and blocked acceleration series.

Since four of the five animals represented in the group data were tested with a low-to-high sequencing of acceleration frequencies, it is

important to note that the frequency-dependent responses were not affected by the order in which the acceleration frequencies were applied. Several examples of individual animal data will now be presented to illustrate this point, and to demonstrate the repeatability of results.

Individual Animal Responses (Examples)

One of the animals represented in the group data was tested with a random sequencing of the acceleration frequencies for both the nonblocked and blocked series. Since aortic pressure has been viewed as the controlled variable and therefore of primary interest, this animal's AP response is shown in Figure 13. An increase in AP mean from control levels is seen in both the nonblocked and blocked runs during acceleration, indicating the overall systemic pressor response reported for the group (Figure 6). A comparison of nonblocked and blocked AP amplitude shows evidence of reflex barostatic regulation up to about 0.1 Hz, and a peaking of blocked AP amplitude in the range of 0.03 to 0.06 Hz. Both nonblocked and blocked AP phase indicate approximately a 180° lag of aortic pressure oscillations with respect to acceleration. All of these features of AP response are similar to those seen in the group data

A second animal in the group was tested with both low-to-high and high-to-low sequencing of the acceleration frequencies in the blocked state (the former having been used in the compilation of the group data). For this animal the DRVP and AF responses for low-to-high and high-to-low frequency sequencing are compared in Figures 14 and 15. First of all, it can be seen that the order in which the frequencies are applied to the animal has essentially no bearing on the frequency-

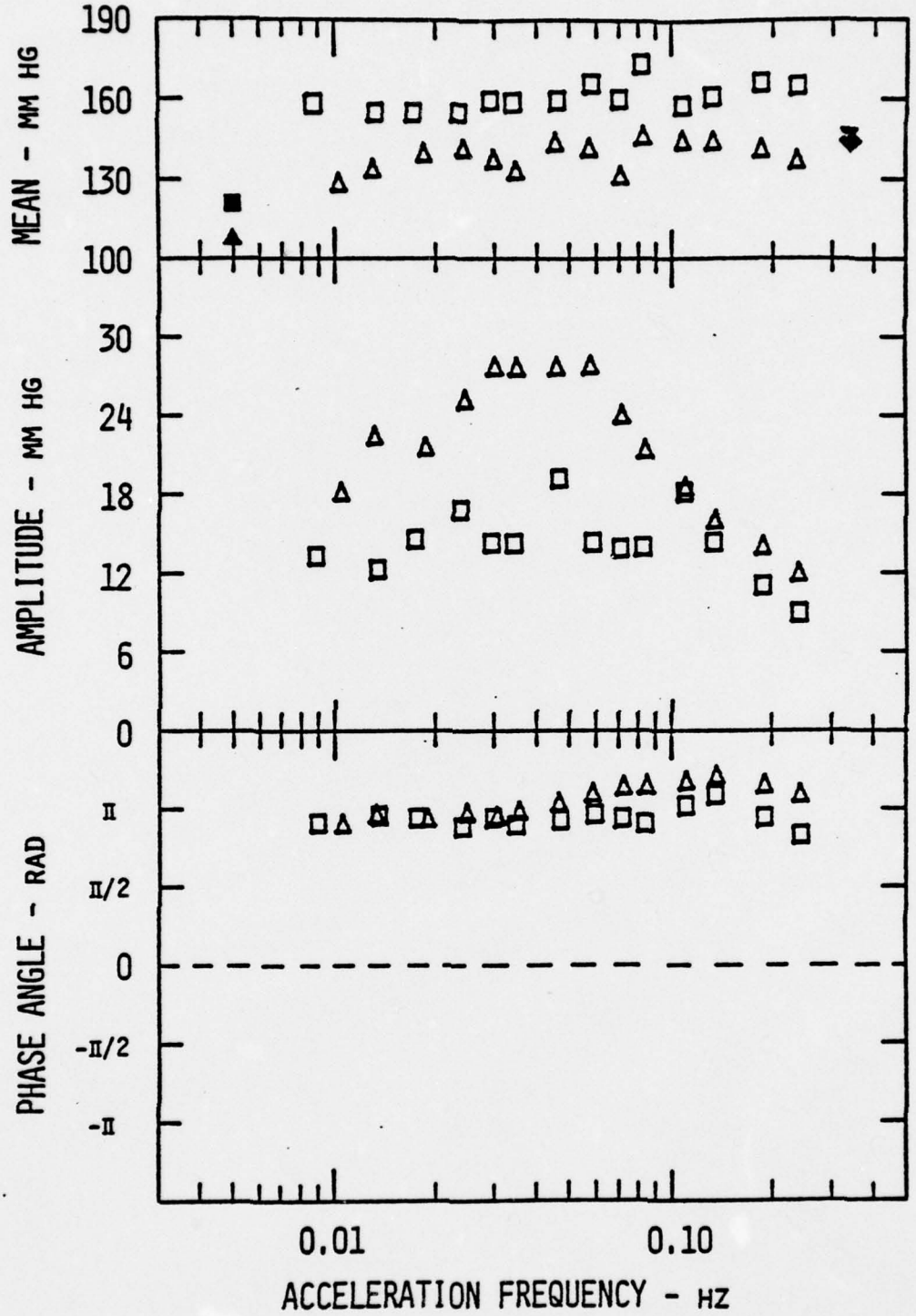


Fig. 13. AORTIC PRESSURE: mean, amplitude and phase of the first Fourier component with respect to acceleration frequency (□ unblocked, △ autonomic blockade, ■ ▲ control and ◆ ▼ recovery values, ⁝ ± SEM) for dog no. 1984 (random sequence of acceleration frequencies).

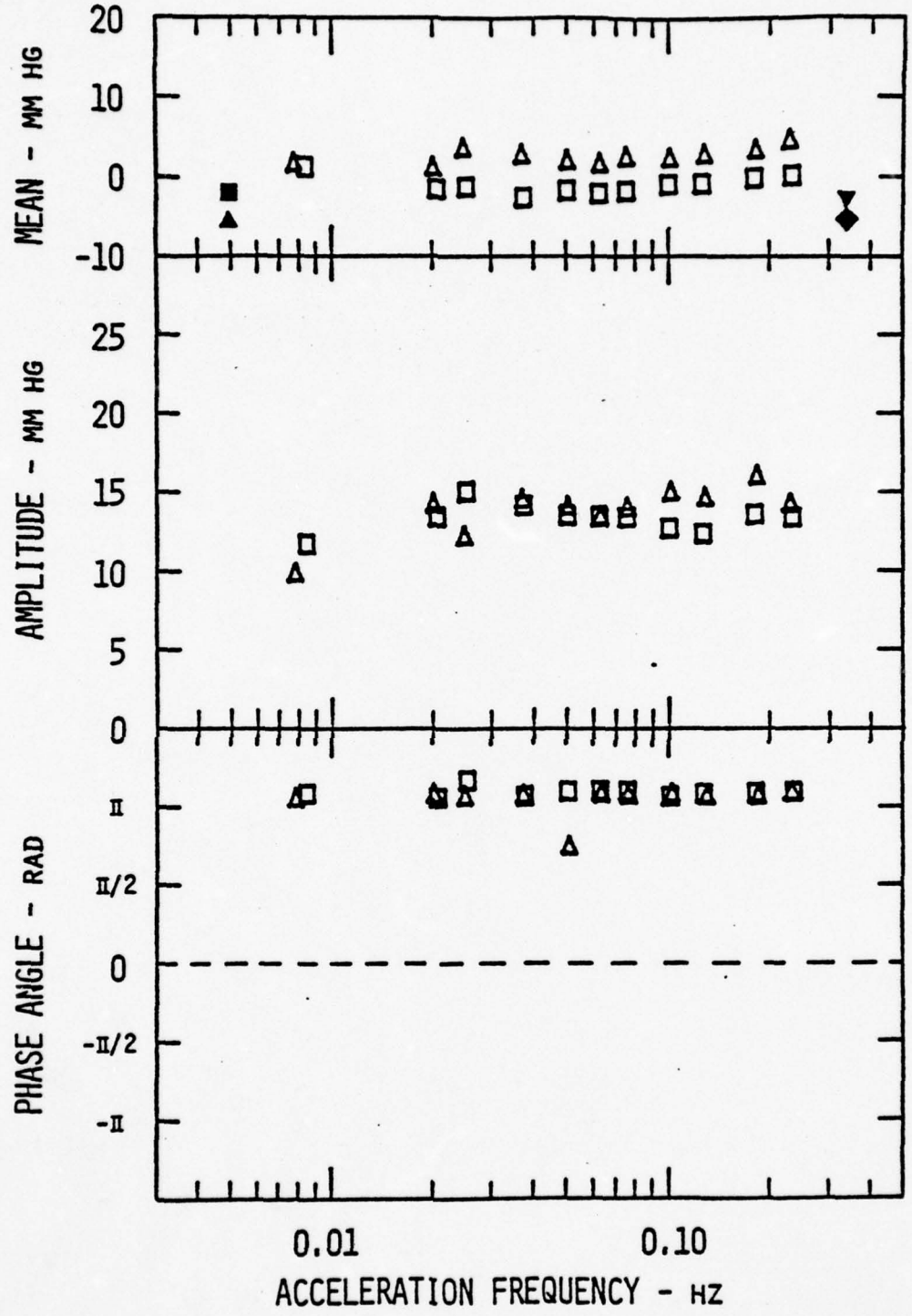


Fig. 14. AUTONOMICALLY BLOCKED DIASTOLIC RIGHT VENTRICULAR PRESSURE: mean, amplitude and phase of the first Fourier component with respect to acceleration (□ low-to-high and △ high-to-low frequency sequence, ■▲ control and ◆▼ recovery values) for dog no. 1673.

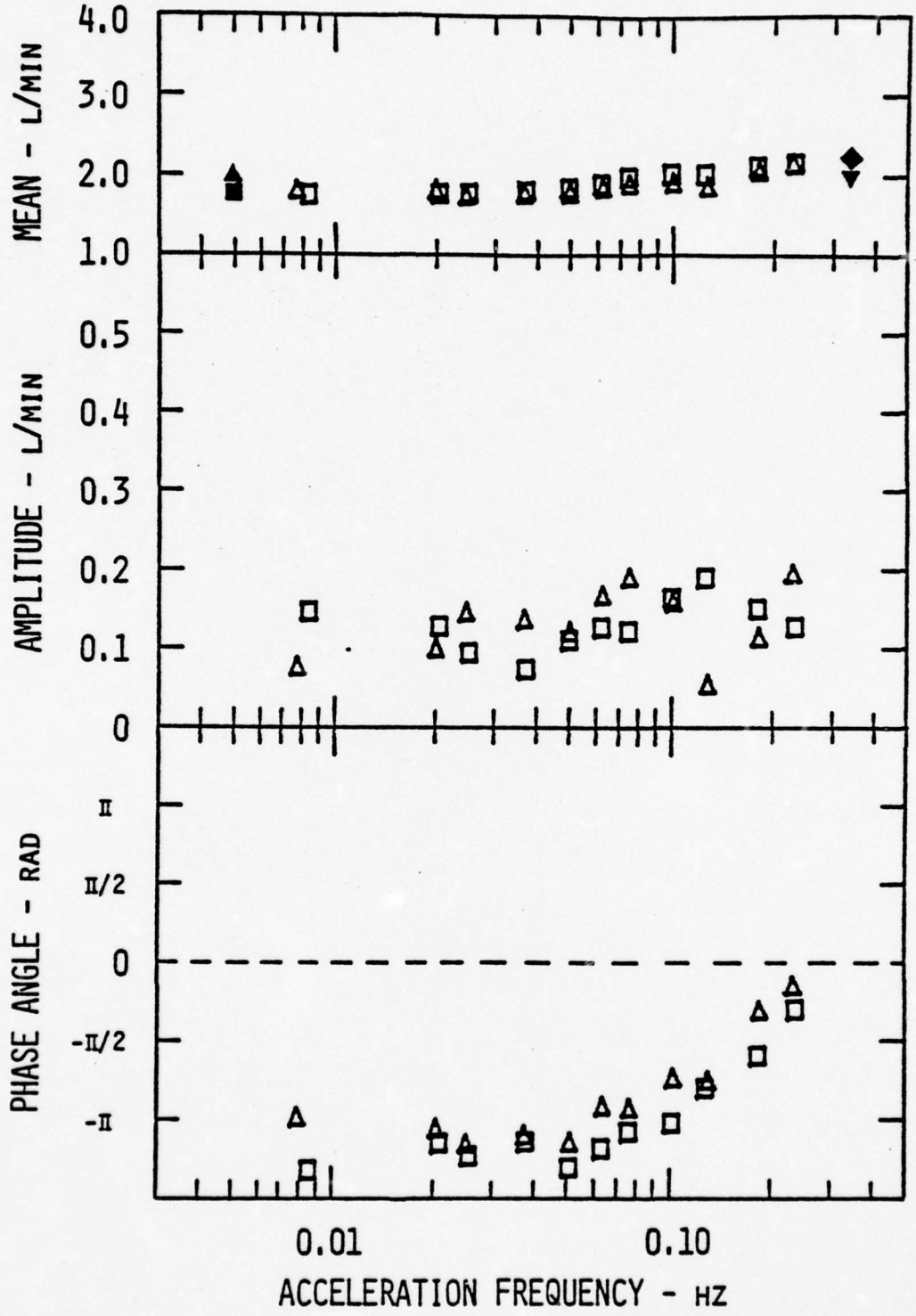


Fig. 15. AORTIC FLOW: mean, amplitude and phase of the first Fourier component with respect to acceleration (□ low-to-high △ and high-to-low frequency sequence, ■ ▲ control and ◆▼ recovery values) for dog no.1673.

dependent behavior of the responses. A 5 - 7 mm Hg increase in DRVP mean (Figure 14) from the control/recovery values was seen during the acceleration series, again indicating the overall systemic pressor response mentioned previously. The values of DRVP amplitude and phase were frequency-invariant, as noted in the group data (Figure 8). The response of AF (Figure 15) for this animal is also similar to the blocked group response (Figure 10). The response of AF mean tended to increase with increasing frequency, AF amplitude was basically frequency-invariant, and AF phase exhibited a progressive phase lag at higher frequencies. In addition to showing that the measured responses are not dependent upon the order in which frequencies are run, these data demonstrate that the results are repeatable in the same animal.

The group data presented in this chapter indicate a significant neurally-mediated response of cardiac and vascular mechanisms during exposure to low frequency, whole body acceleration. It is important to recognize, however, that these reflex mechanisms are probably responding to intravascular pressure/flow disturbances produced by the acceleration stress and not the acceleration itself. Therefore, in order to model the barostatic reflex activity seen in the experimental data, one must look at the cardiac and vascular control mechanisms from the standpoint of pressure as the sensed, as well as controlled variable. This will be done in the following chapter.

CHAPTER VII

RESPONSE MODELING

In addition to providing heretofore unavailable information about the low frequency dynamics of integrated barostatic cardiovascular regulation during exposure to a natural noninvasively-applied stress, the results of these studies constitute a quantitative data base from which to mathematically model the major components of the baroreflex control network.

Although there have been numerous attempts to model the total cardiovascular system, starting with models of the noncontrolled passive circulatory network[50,51] and extending to more complex models which include baroreflex control elements[52,53], these models have several shortcomings. The less complex passive circulatory models are not directly applicable to the study of dynamic barostatic regulation, because they contain no provisions for baroreflex control elements. The more complex controlled models generally require extensive "dedicated" analog, digital or hybrid computing facilities, that are not widely available, in order to run simulations. In addition, because the more rigorous models are based upon the detailed functional relationships between passive and active cardiovascular components, an unwieldly number of parametric manipulations would probably be necessary to use such models in a simulation of cardiovascular response to a noninvasive, total-circulatory (i.e. distributed) forcing function such as whole body acceleration. As a compromise between these two

types of models, the approach taken in the present study was to derive empirical linear transfer functions to describe the general reflex action of the major cardiac and vacular control components, within the context of normal integrated barostatic regulation. Although not part of the present work, it was intended that these transfer functions would be incorporated into an existing passive circulatory model[51] which is part of an available simulation package[54] designed to run on a PDP-11/10 minicomputer system having limited core storage capabilities.

The transfer functions to be presented are generally of proportional or proportional-plus-derivative second-order form, with some having exponential transportation lag terms. Higher order terms were not included in the derived transfer functions for several reasons: 1) As noted in the background review, most often the low frequency dynamics of the baroreflex mechanisms have been adequately modeled as first or second-order controllers, with input/output time lag terms in particular instances. In addition, the amplitude/phase data in the present study seem to reflect roughly a second-order type of response. Consequently, it was felt that higher order terms would not be necessary, to achieve a reasonable approximation of the experimental responses. 2) Also, the eventual incorporation of the transfer functions into a total cardiovascular model would be made somewhat more difficult by the addition of higher order terms.

The general complex plane (s plane) representation for a proportional-plus-derivative second-order controller with time lag is of the form:

$$\frac{O(s)}{I(s)} = \frac{G_p + G_d s}{1 + 2\zeta\left(\frac{s}{\omega_n}\right) + \left(\frac{s}{\omega_n}\right)^2} \exp(-\tau s) \qquad (7\text{-}1)$$

where

$O(s)$ = the output variable

$I(s)$ = the input variable

s = the complex quantity $j\omega$, where ω is frequency (rad/sec)

G_p = proprotional gain coefficient

G_d = derivative gain coefficient

ζ = damping coefficient (nondimensional)

ω = undamped natural (resonant or corner) frequency (rad/sec)

τ = input/output time lag (sec)

When the input, or forcing function to the controller is sinusoidal (as in the present study) it is more convenient to represent the input/output relationship given by Equation 7-1, in its equivalent magnitude/phase form, i.e.:

$$\text{Magnitude} = \left[\frac{G_p^2 + (G_d\omega)^2}{\left(1 - \left(\frac{\omega}{\omega_n}\right)^2\right)^2 + \left[2\zeta\left(\frac{\omega}{\omega_n}\right)\right]^2} \right]^{1/2} \tag{7-2}$$

$$\text{Phase} = \text{Tan}^{-1}\left[\frac{\left(1 - \left(\frac{\omega}{\omega_n}\right)^2\right) G_d\omega - 2\zeta\left(\frac{\omega}{\omega_n}\right) G_p}{\left(1 - \left(\frac{\omega}{\omega_n}\right)^2\right) G_p + 2\zeta\left(\frac{\omega}{\omega_n}\right) G_d\omega} \right] - \tau\omega \tag{7-3}$$

This representation of Equation 7-1 is directly compatible with the format in which the experimental results were presented in the preceding chapter. In other words, Equation 7-2 represents the ratio

AD-A069 952 KENTUCKY UNIV LEXINGTON WENNER-GREN RESEARCH LAB F/G 6/5
THE CAUSES OF DECREMENTS IN AIRCREW PERFORMANCE: PHYSIOLOGICAL --ETC(U)
SEP 78 C F KNAPP, J M EVANS, D R RANDALL F44620-74-C-0012
AFOSR-TR-79-0676 NL

UNCLASSIFIED

2 OF 2

AD A069952

END
DATE FILMED
7-79
DDC

of the amplitude of output (response) oscillations to the amplitude of the input oscillations at frequency ω. Similarly, Equation 7-3 represents the phase lag between the input and output waveforms. Therefore, for example, the blocked AP amplitude/phase data from Figure 6 could be (and were) fitted directly to Equations 7-2 and 7-3 to derive an acceleration-to-arterial blood pressure transfer function. Before proceeding, it should be noted that by dropping given terms in Equation 7-2 and 7-3 one may obtain lower-order transfer relationships. (e.g., setting $G_d = 0$ and $\tau = 0$ yields a simple second-order controller).

As mentioned at the conclusion of the preceeding chapter, it is important to recognize that the baroreflex control mechanisms respond to intravascular blood pressure disturbances produced by the applied acceleration stress, not to the acceleration itself. Therefore, in order to model the barostatic reflex activity seen in the experimental results, the cardiac and vascular control mechanisms had to be viewed from the standpoint of pressure as the sensed, as well as controlled variable.

Acceleration-Induced Pressure Disturbances

The first step in this process is to develop a transfer function for the arterial pressure disturbances generated by whole body acceleration within the passive nonreflexive cardiovascular system. These passively produced arterial pressure disturbances are given by the blocked AP amplitude/phase data in Figure 16, and are important because they represent: 1) the acceleration-to-arterial pressure response characteristics that must be realized in a passive, non-controlled circulatory model before baroreflex components can be added, and 2) those pressure changes which the baroreflex mechanisms

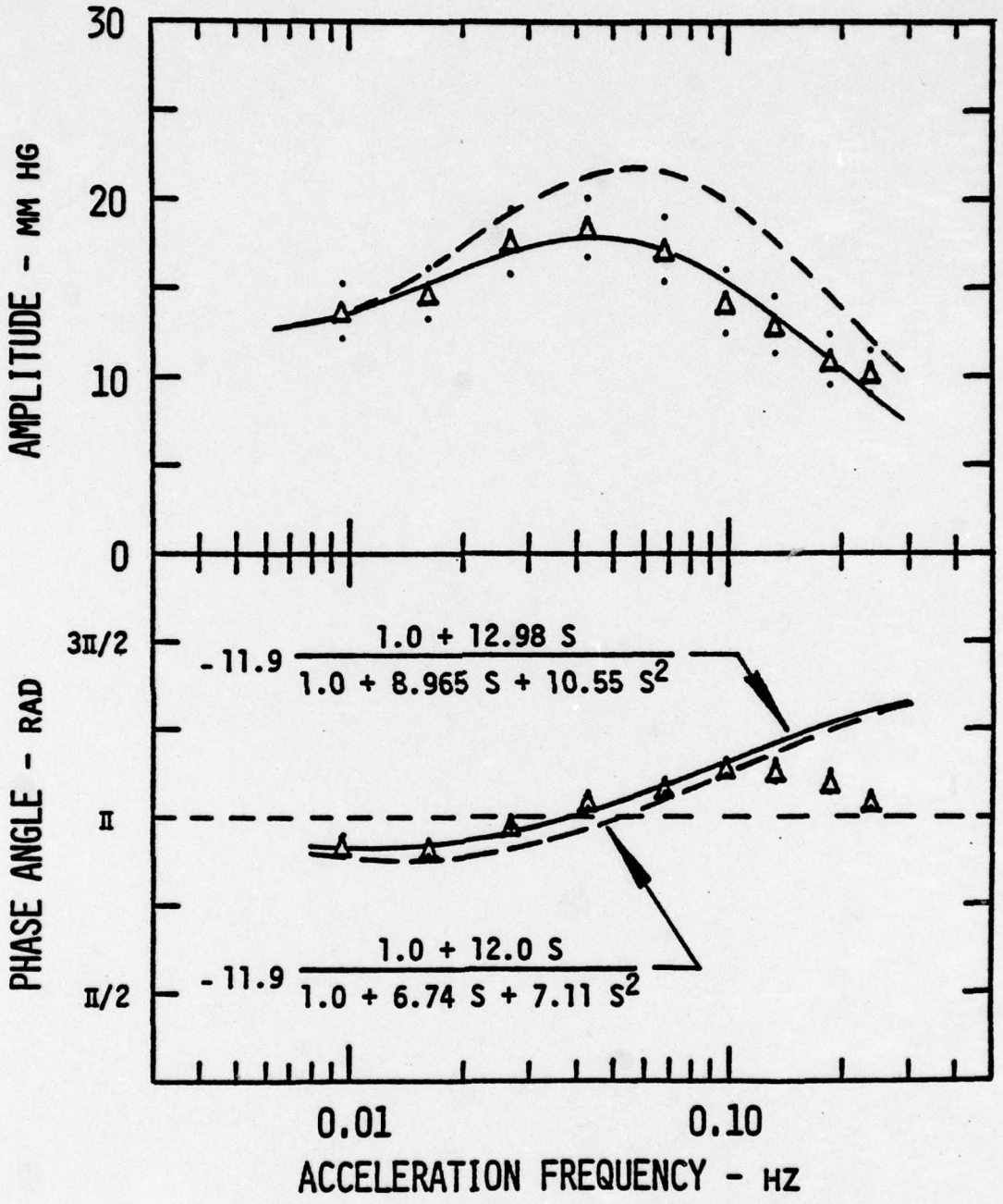


Fig. 16. AUTONOMICALLY BLOCKED AORTIC PRESSURE RESPONSE: —— the author's single-zero double-pole transfer function fitted to the experimental Fourier amplitude and phase values (Δ , ⁝ ± SEM), and – – – the single-zero double-pole acceleration-to blood pressure transfer function for humans from Gillingham [25].

should act to minimize (i.e., the "open loop" input to the baroreceptors). These data were least squares fitted with an acceleration-to-arterial pressure transfer function of the form:

$$\frac{AP}{ACC}(s) = -5.85 \frac{1.0 + 12.9s}{1.0 + 8.965s + 10.5s^2} \qquad (7\text{-}4)$$

where

AP = blocked aortic (artieral) pressure

ACC = input acceleration, of 2G amplitude

This proportional-plus-derivative second order response indicates a highly damped ($\zeta = 2.76$) system with an undamped natural frequency of 0.049 Hz. A similar transfer function was derived by Gillingham[25] in studies of eye-level blood pressure changes in humans exposed to SCAMs (Ref. Chapter II, p. 21). Gillingham's transfer function was of the form:

$$\frac{AP}{ACC}(s) = -16.2 \frac{1.0 + 12.0s}{1.0 + 6.74s + 7.11s^2} \qquad (7\text{-}5)$$

also indicating a highly damped ($\zeta = 2.53$) response, with a higher undamped natural frequency of 0.06 Hz. For purposes of comparison with Equation 7-4 (present results), Equation 7-5 is also plotted in Figure 16, with a suitable adjustment of the leading gain factor in order to match the low frequency asymptotes. It can be seen that while Equation 7-4 matches the experimental blocked AP amplitude data reasonably well, the phase fit it good only up to about 0.1 Hz. Gillinghan reported a similar mismatch of his predicted and experimental phase data above 0.1 Hz, which was reduced by the addition of a second-order term in the numerator of his derived transfer function (Equation 7-5). Consequently, the addition of a second-order term in the numerator of Equation 7-4 would probably enhance its fit to the

present experimental phase data.

Although the blocked AP response represents the pressure disturbance generated (by whole body acceleration) within the passive noncontrolled arterial system and is, therefore, an approximation of the open loop input to the baroreceptors, it was not the input seen by the baroreceptors during the nonblocked acceleration tests. In the nonblocked tests, since the barostatic regulatory mechanisms are functioning in a closed-loop integrated fashion, the input to the baroreceptors is more properly approximated by the nonblocked AP response. As a result, the derivation of transfer functions for baroreflex action of the individual cardiac and vascular control mechanisms was approached from the standpoint of nonblocked AP response as the input variable.

Systemic Vascular Mechanisms

The relative aortic pressure-to-effective systemic resistance response was calculated for individual animals. The group data were then compiled and are presented in Figure 17. The top panel of Figure 17 shows the ratio of nonblocked ER mean to nonblocked AP mean, and is included to emphasize the high frequency decrease of ER mean reported earlier in the presentation of results. The relative ER amplitude was calculated as the difference between nonblocked and blocked ER amplitudes divided by the nonblocked AP amplitude. The difference between nonblocked and blocked ER amplitudes was used in this computation, because it was felt that this was a better index of the active baroreflex-mediated systemic vascular response than nonblocked ER amplitude alone (Ref. Chapter 6, p. 50-54). The relative

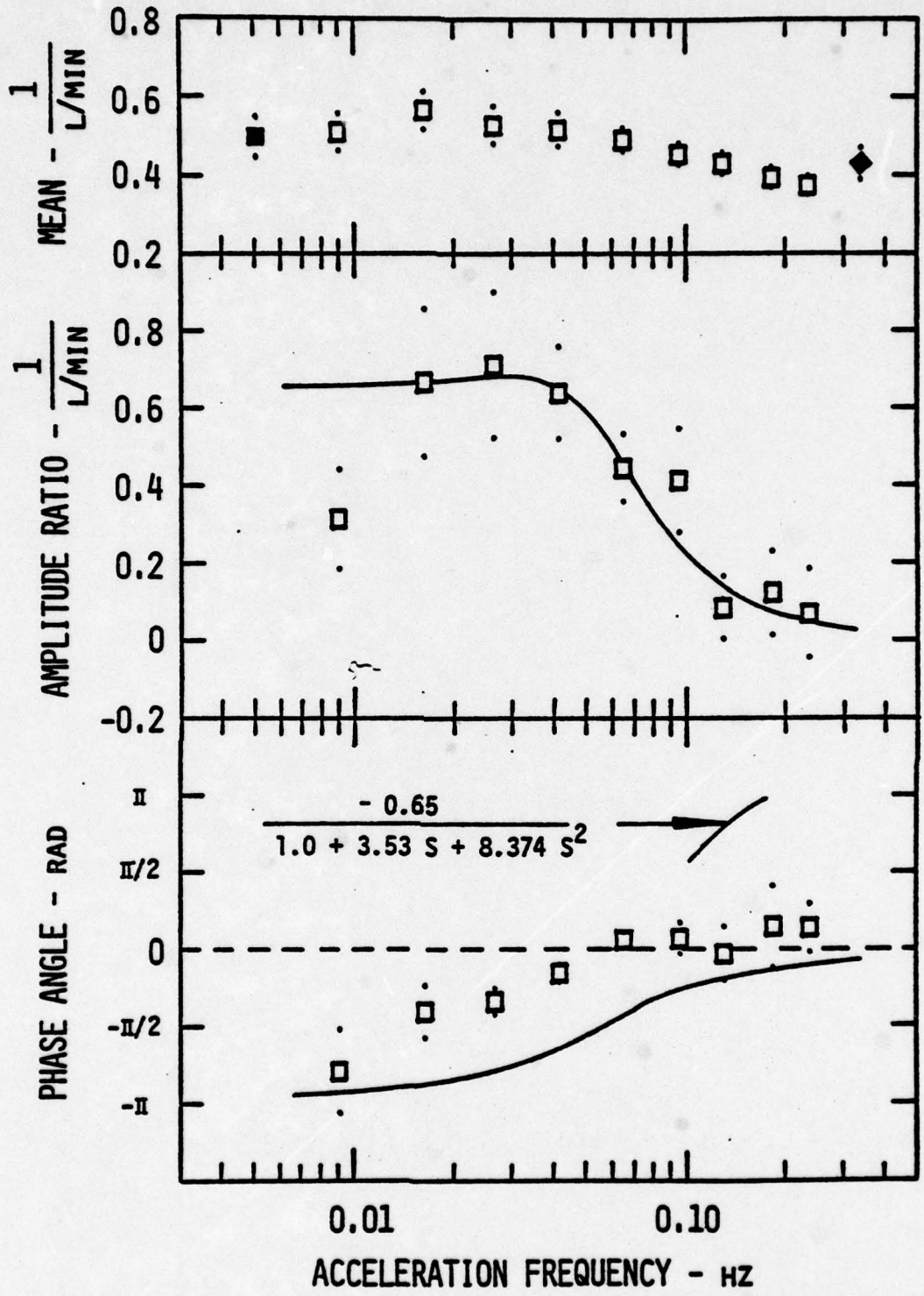


Fig. 17. RELATIVE RESISTANCE / AORTIC PRESSURE RESPONSE: mean ratio, amplitude ratio and relative phase of the first Fourier components as a function of acceleration frequency, for a group of 5 unblocked animals (■ control and ◆ recovery values, ⁝± SEM).

ER phase, calculated as the difference between nonblocked ER phase and nonblocked AP phase, is also shown in Figure 17. With exception of the lowest frequency (0.009 Hz), it can be seen that the relative ER amplitude data is adequately represented as a critically-damped (ζ = 1.22) second-order response with an undamped natural frequency of 0.055 Hz, of the form:

$$\frac{ER}{AP}(s) = \frac{-0.65}{1.0 + 3.53s + 8.374s^2} \qquad (7\text{-}6)$$

On the other hand, this transfer function yields a predicted relative ER phase that does not match the experimental results. The addition of a time lag term to Equation 7-6 did not significantly enhance the overall fit of the predicted ER phase, and was therefore not included. It is important to note, however, that the damping coefficient and resonant frequency inherent in Equation 7-6 fall well within the range of values reported by previous investigators who studied the open loop carotid sinus/arterial pressure response. The present data suggest that the arterial pressure-to-systemic resistance transfer relationship is higher than second-order and that extra higher order terms need be added to Equation 7-6 in order to obtain an accurate predictive transfer function for the vascular component of the baroreflex control network.

Several investigators[55,56] have verified the existence of sympathetic afferent mechanoreceptors in the right atrium and pulmonary artery, and suggested that these may elicit efferent pressor responses in the peripheral vasculature, in response to changes in venous return or right heart pressure. Taking this suggestion and noting that whole body acceleration produces significant right atrial pressure changes (Figure 8), an attempt was made to derive a DRVP-to-ER transfer

relationship. Using nonblocked DRVP instead of nonblocked AP as the input variable, a relative ER was computed, as described earlier. The experimental data based upon this computation are presented in Figure 18, along with a fitted transfer function of the form:

$$\frac{ER}{DRVP}(s) = \frac{-(0.64 + 1.924s)}{1.0 + 3.006s + 19.545s} \exp(-3.219s) \qquad (7\text{-}7)$$

Equation 7-7 represents an underdamped ($\zeta = 0.68$) second-order response with an undamped natural frequency of 0.036 Hz and an input/output time lag of 3.219 sec. Although this transfer function does not have a strict functional basis, physiologically speaking, it could be used as a phenomenological predictor of effective systemic resistance (ER) responses for frequencies up to 0.1 Hz.

Two general observations may be made at this point regarding these efforts to model the experimental ER responses: 1) either baroreflex control of integrated, overall systemic resistance activity must be represented by a higher than second-order controller, or 2) aortic arch pressure alone is not a suitable input variable for modeling the systemic vascular mechanisms.

Cardiac Mechanisms

A relative HR response was computed using the nonblocked AP and HR responses as the input and output functions respectively. The group relative HR data are presented in Figure 19. The slight high frequency increase in relative HR mean probably indicates a reflex response to the high frequency decrease in ER mean (Figures 9 and 17). Relative HR amplitude exhibits a significant peaking response at about 0.06 Hz. A comparison of the phase data in Figure 11 and Figure 19 shows that while HR appears to be leading acceleration at the lowest

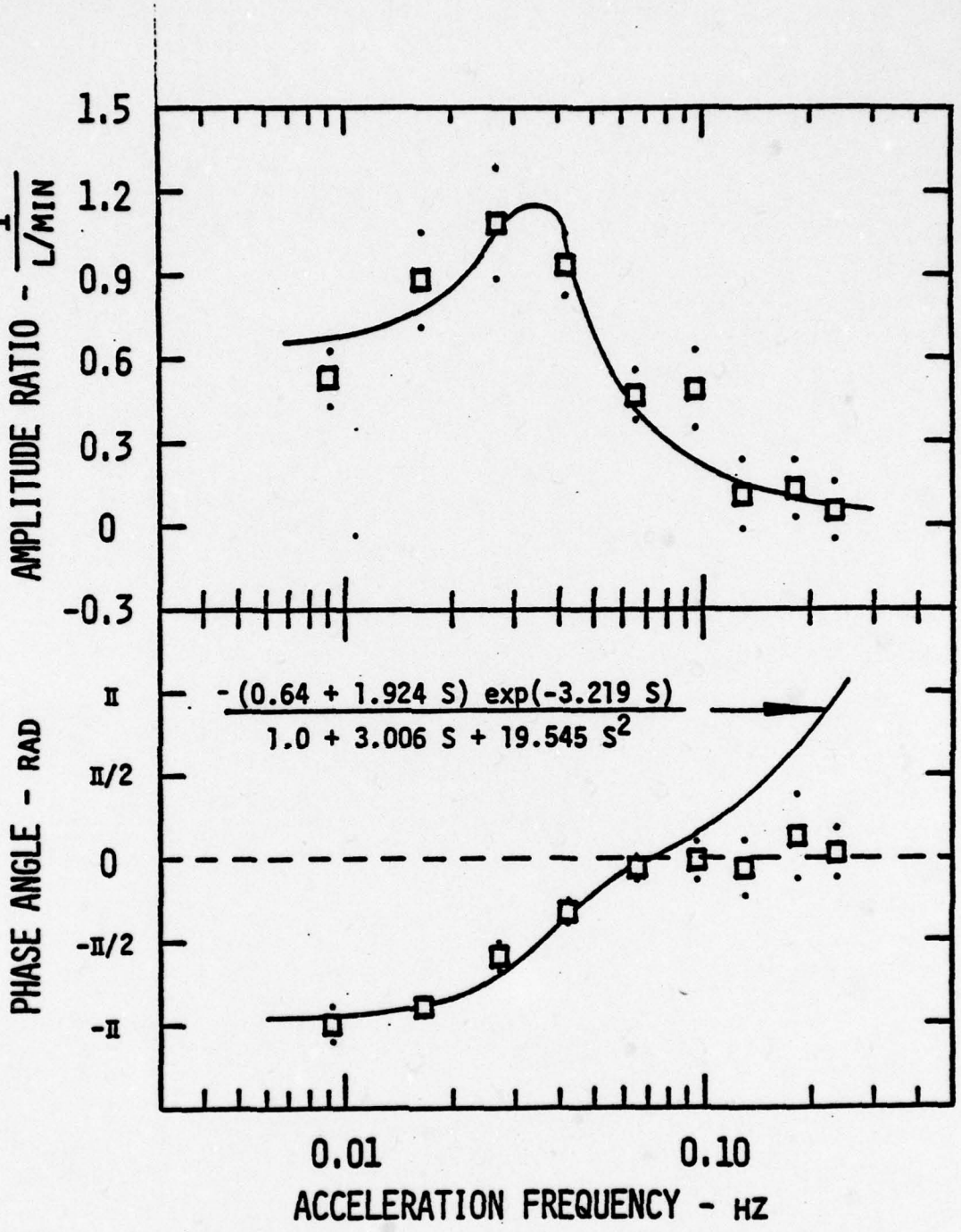


Fig. 18. RELATIVE RESISTANCE / DIASTOLIC RIGHT VENTRICULAR PRESSURE RESPONSE: amplitude ratio and relative phase of the first Fourier components as a function of acceleration frequency, for a group of 5 unblocked animals (■ control and ◆ recovery values, ⁝± SEM).

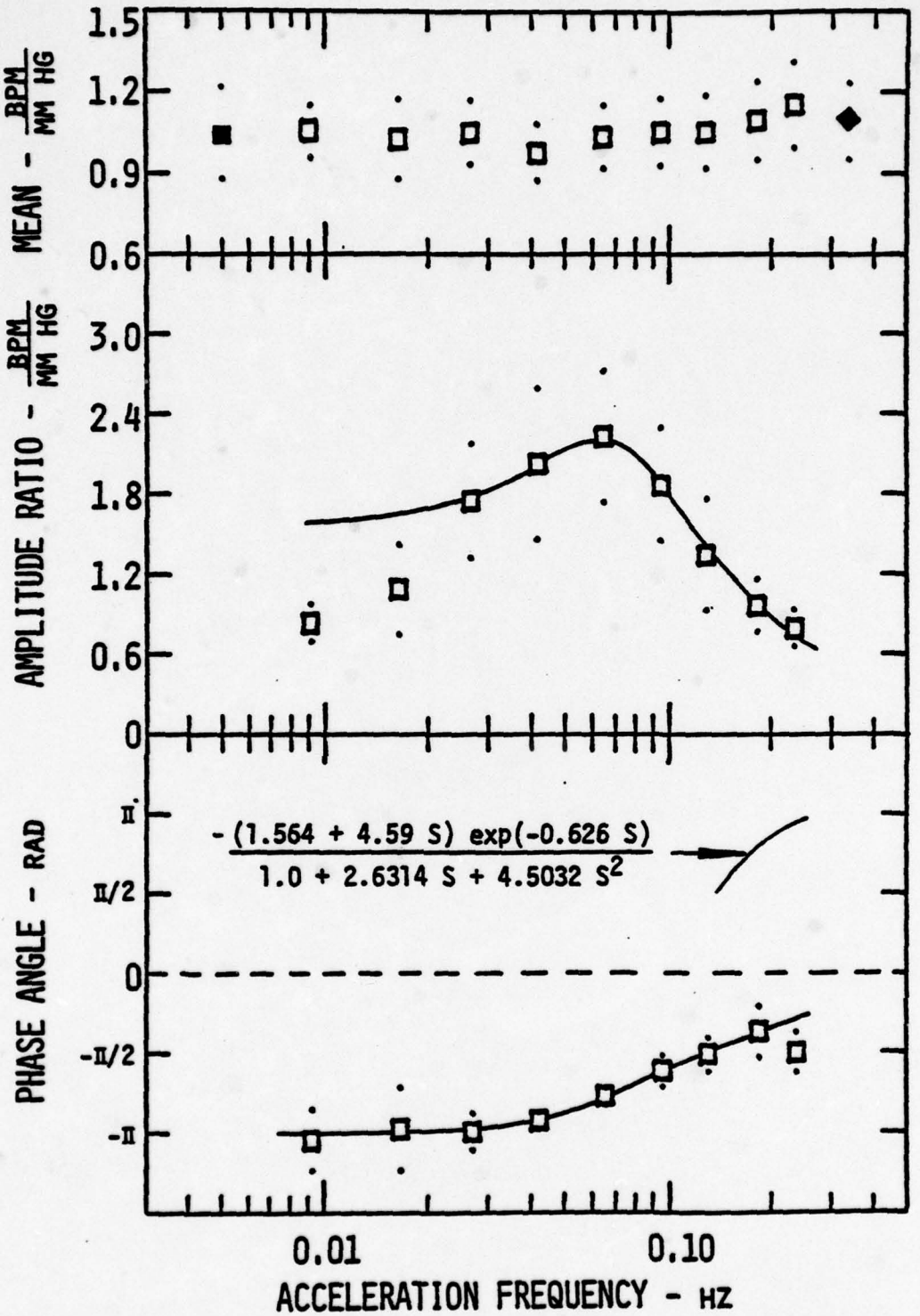


Fig. 19. RELATIVE HEART RATE / AORTIC PRESSURE RESPONSE: mean ratio, amplitude ratio and relative phase of the first Fourier components as a function of acceleration frequency, for a group of 5 unblocked animals (■ control and ◆ recovery values, ± SEM).

frequencies, it is actually in "proper" phase with respect to AP, to which it responds. In other words, at the low acceleration frequencies HR increases as AP decreases. It was found that the relative HR amplitude/phase response (Figure 19) could be represented reasonably well as a second-order controller of the form:

$$\frac{HR}{AP}(s) = \frac{-(1.564 + 4.59s)}{1.0 + 2.6314s + 4.5032s^2} \exp(-0.626s) \qquad (7\text{-}8)$$

which has an undamped natural frequency of 0.075 Hz, a damping doefficient $\zeta = 1.24$ and a time delay of 0.626 sec. The proportional-plus-derivative input term (numerator) in Equation 7-8 was suggested by the work of Katona (1965)[57] who demonstrated that the afferent baroreceptor firing rate could be modeled with both mean pressure (proportional term) and pulse pressure (derivative term) as input variables. Allison (1969)[6] reported a 0.4-1.0 sec time delay between step changes in pressure in the isolated aortic arch (i.e., arch baroreceptors) and reflex changes in heart rate. Similarly, Scher and Young (1963)[14] saw a 0.6-1.2 lag between step changes in carotid sinus pressure and heart rate response. Consequently, the 0.626 sec time lag term in Equation 7-8 would seem justified. Enhancement of the low frequency fit of Equation 7-8 to the relative HR amplitude (Figure 19) could probably be achieved by the addition of a second order term on the input side of the derived transfer function.

As noted in the presentation of results, the response of SF amplitude (Figure 12) appears to be largely frequency-invariant from 0.008-0.23 Hz. This, along with the fact that there was no significant difference between nonblocked and blocked SF phase, indicates that the overall SF response to whole body acceleration is not effected

neurally, but is rather the result of passive nonneural factors. Comparing Figures 8 and 12, and noting that oscillations in DRVP and SF are in phase (0^o phase difference) at the lower frequencies, one may conclude that the SF response is probably determined primarily by changes in venous pressure or venous return. The progressive lagging response of SF phase at higher frequencies can be explained (and modeled) as a right-to-left heart time lag phenomenon. The nonblocked and blocked SF phase data from Figure 12 were replotted on a linear frequency scale, Figure 20, and fitted with a least squares regression line. The results show that the response of SF phase can be modeled by a simple time delay of about 2.0 sec, which is in good agreement with the right-to-left heart lag of at least three cardiac cycles reported by Franklin et al. (1962)[37] for the response to a rapid right atrial infusion of saline. Consequently, a passive noncontrolled model of the cariovascular system should include a cardiopulmonary component which yields a passive DRVP to SF transfer relationship of the form:

$$\frac{SF}{DRVP}(s) = G_p \exp(-2.177s) \qquad (7\text{-}9)$$

with an approximate value of $G_p = 0.12$ (ml/b)/mmHg, based upon the blocked DRVP and SF amplitude/phase data from Figures 8 and 12.

In conclusion, the present efforts to model the response characteristics of the cardiac and vascular baroreflex mechanisms have shown that: 1) While there is significant frequency-dependent neural control of the systemic vascular mechanisms below 0.15 Hz, this control can not be satisfactorily modeled as a second order response based upon aortic pressure as the input, 2) Neural control of heart rate is frequency-dependent below 0.23 Hz, and can be adequately

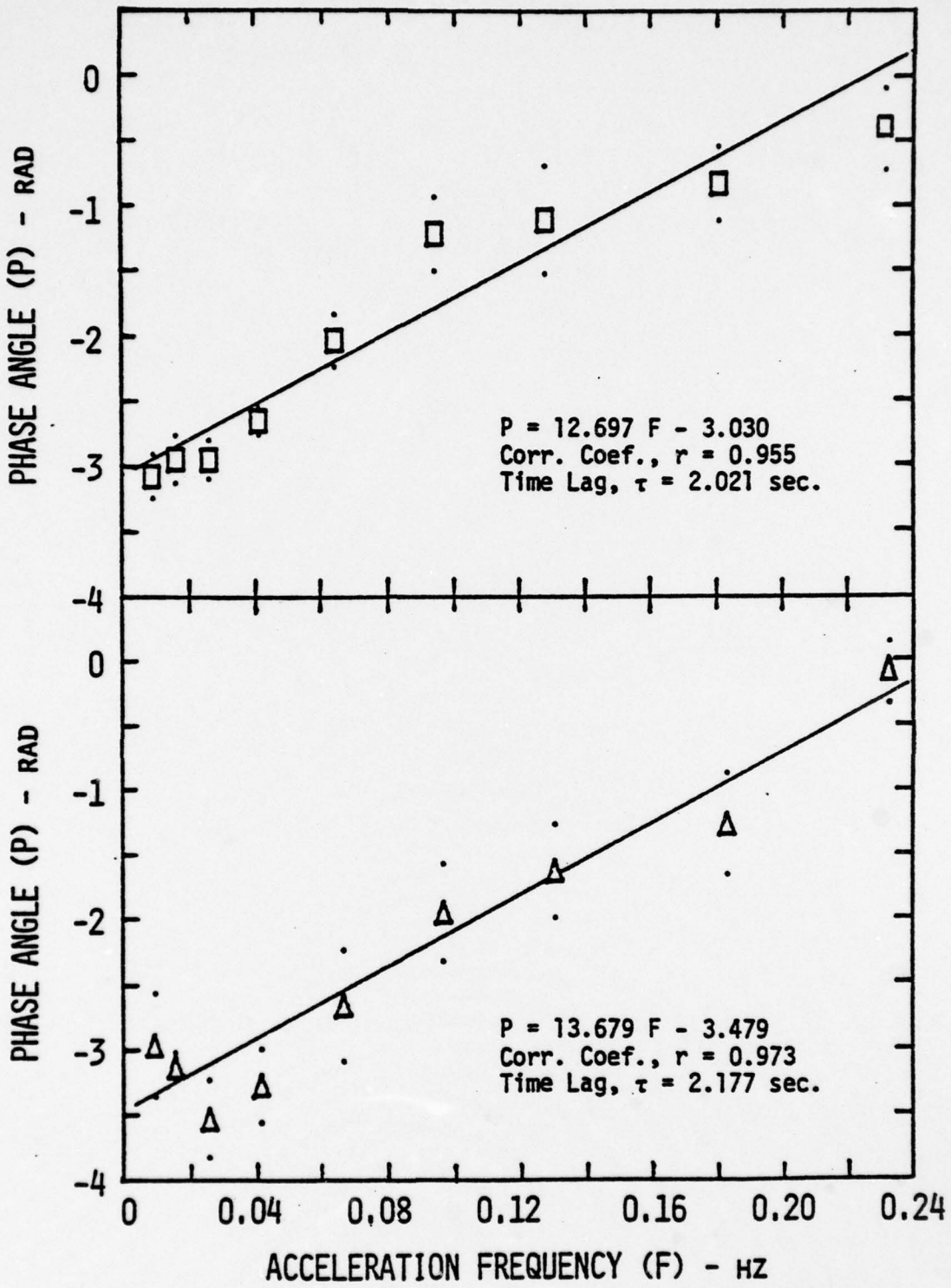


Fig. 20. STROKE FLOW: relative phase of the first Fourier component as a function of acceleration frequency (□ unblocked, △ autonomic blockade, ⁚ ± SEM, and —— least squares linear fit) for a group of 5 animals.

modeled by a second-order time lag controller, and 3) Stroke flow response to whole body acceleration is predominantly influenced by passive venous pressure changes.

CHAPTER VIII

DISCUSSION

The purpose of this study was to investigate and model the low frequency dynamics of integrated barostatic cardiovascular regulation using sinusoidal whole body acceleration as a noninvasive forcing function to the cardiovascular system. Chronically instrumented and unanesthetized canines were exposed to spinal axis acceleration at frequencies below 1.0 Hz and the response of specific cardiovascular variables measured. The participation of neurally-mediated cardiac and vascular baroreflex mechanisms in the overall response was evaluated by comparing the subjects' responses in a reflexive (neurally active) and nonreflexive (neurally blockaded) condition. Transfer functions were then derived to describe the passive acceleration-induced intravascular pressure disturbances and the reflex control of the major baroreflex mechanisms.

The results of the present study indicate that the dynamic characteristics and integrated function of the baroreflex mechanisms, during exposure to noninvasively-applied whole body acceleratory loadings, are very similar to the results of previous studies where the "open loop" frequency response of the cardiac and vascular control mechanisms was determined using acture pressure stimulation of aortic arch and carotid sinus baroreceptors. There were, however, quantitative differences in the degree of effective pressure regulation measured in the present study and what would be predicted from previous work.

Arterial Pressure Regulation

Refering to Figure 6, with the reflex action of the neurally-mediated barostatic mechanisms pharmacologically blocked, the resultant AP oscillations represent the passive acceleration-induced pressure changes which the cardiac and vascular control mechanisms should act to minimize in the nonblocked animal. A comparison of the amplitude of the nonblocked and blocked AP oscillations, Figure 7, indicates that the barostatic control network is able to achieve a 30 - 35% attenuation of the passive AP oscillations for frequencies up to 0.07 Hz. Above 0.10 Hz no effective regulation of AP was seen. These general features of the overall control of AP are in good agreement with the results of previous investigators[10,14,16] who have studied (specifically) carotid sinus control of arterial pressure and reported a critically-damped (flat) second-order type of response with a corner frequency of 0.04 - 0.06 Hz. Consequently, the results of these previous studies indicate that carotid sinus reflex is unable to generate significant compensatory arterial pressure responses for input frequencies above around 0.1 Hz. Dynamic carotid sinus-to-systemic arterial pressure "open loop" gains of 2.0 - 6.0 were reported by Scher and Young (1963)[14] in dogs, while Grodins (1963)[7] reported a similar value of about 1.8. These gain values (G) would suggest that during normal "closed loop" operation the carotid sinus reflex should be able to achieve a 64 - 86% attenuation of the "open-loop" pressure disturbance [attenuation = G/(1+G)]. There is a significant difference between these predicted values and the 30 - 35% attenuation (G = 0.43 to 0.54) seen in the present study. Based upon evidence from the present study, this discrepency can be explained by the response of acceleration-

induced cardiac output fluctuations, and the interaction between cardiac and vascular control mechanisms (which were not factors in these previous studies). This point will be addressed later in some detail.

For reasons stated in Chapter III, the application of the results of these previous studies to predict normal unanesthetized integrated cardiovascular response to natural noninvasive stimuli is unclear; especially since they used localized cardiovascular stimuli to examine isolated components of the barostatic control network in acutely-instrumented anesthetized animals. Consequently, it is felt that the results of the present study provide a better picture of overall dynamic barostatic control under more normal conditions of cardiovascular stress.

Systemic Vascular Control

Since past studies of the dynamic behavior of the carotid sinus/arterial pressure response (preceding discussion) involved the use of vagotomized animals, it was implied (although not reported) that cardiac output was relatively constant, and did not therefore influence measured arterial pressure changes. The "open loop" reflex responses were, therefore, attributed to systemic vascular activity, and should constitute a basis for comparison with the present ER results (Figures 9 and 17). A comparison of nonblocked and blocked ER amplitude in Figure 9 illustrates that there is a significant neurally-mediated systemic vascular component in the dynamic baroreflex response for frequencies up to approximately 0.10 Hz. Using nonblocked AP as the input variable, a relative ER response was computed, as shown in

Figure 17. For all except the lowest input frequencies (about 0.01 Hz), the relative ER amplitude response could be accounted for with a critically-damped (ζ = 1.22) second-order model, Equation 7-6, with an undamped natural frequency of 0.055 Hz. While this transfer relationship is in good agreement with the results of previous studies of the open-loop carotid sinus/arterial pressure response, it predicts relative phase angles that are significantly a lower than those measured experimentally in the present study. A number of factors could explain this discrepancy: 1) Reflex control of the overall systemic vascular response must be represented by a higher-order controller such as the proportional-plus-derivative sensitive third-order model developed by Scher et al. (1967)[16] for composite data concerning the carotid sinus reflex system, 2) Aortic arch pressure alone is not a good index of the input to both the arch and carotid sinus baroreceptors, implying that carotid sinus pressure should have been measured seperately in the present study, or 3) Other sensory inputs, such as those from vestibular sensors or cardiopulmonary mechanoreceptors (Ref. Equation 7-7 and Figure 18) play a singificant role in the response of vascular mechanisms to whole body acceleration stress.

An interesting feature was noted in the frequency-dependence of the mean systemic resistance level (Figures 9 and 17) during whole body acceleration. In both the nonblocked and blocked tests there was an overall mean systemic pressor response at frequencies below 0.04 Hz, with an apparent relaxation of this response at higher frequencies. For the nonblocked tests this trend in ER mean would probably be attributed to the "baroreceptor rectification" phenomenon reported by Scher and Young (1963)[14] and others[8,17,18,32]. However, since

this effect was also seen in the blockaded tests, several possibilities arise: 1) The phenomenon is due to nonneural, passive or autoregulary influences or 2) It is a "baroreceptor-rectification" effect which activates mechanisms that are not adrenergic or cholinergic in nature. Related, but as yet uncompleted, studies by others in this laboratory are currently in progress to resolve the factors leading to this response.

Cardiac Control

While the responses of the cardiac mechanisms (heart rate and stroke flow) were treated individually in the presentation of results (Chapter VI) and modeling (Chapter VII), several important points are illustrated in the overall cardiac output response (Figure 10). Comparing nonblocked AP and AF phase (Figures 6 and 10), it can be seen that below 0.02 Hz, AF is decreasing at the same time AP is decreasing (i.e., they are roughly in phase), so that cardiac output does not augment or assist ER mechanisms in controlling aortic pressure for this frequency range. This indicates that for frequencies below 0.02 Hz changes in systemic resistance are the major contributing factor to the minimization of acceleration-induced pressure changes (Figure 6). For frequencies between 0.04 and 0.10 Hz this situation is apparently reversed. Comparing Figures 6, 9, and 10 it can be seen that within this range, AF and AP are approximately 180^{o} out of phase while ER and AP are in phase indicating that the AF response is acting to counter changes in AP, while the ER response is augmenting AP. Consequently, for frequencies from 0.04 to 0.10 Hz arterial pressure regulation is achieved principally by changes in cardiac output. Between 0.02 and 0.04 Hz, where some degree of reflexive barostatic

regulation is also seen, both cardiac output and vascular resistance changes presumably are contributing factors. Because previous investigators have not looked at integrated baroreflex control, this type of interaction between cardiac and vascular mechanisms has not been reported in the past.

Another feature of the overall cardiac output response to note in Figure 10 is the tendency of AF mean to increase with frequency above 0.05 Hz in both the nonblocked and blocked states, as compared to low frequency levels. This response could be caused by either, or both, of the following: 1) decreased left ventricular output impedance (decrease in ER mean, Figure 9) or 2) an increase in the relative level of venoconstriction (increased DRVP mean, Figure 8). The net effect of the response of ER mean and AF mean is a roughly constant level of AP mean (Figure 6) throughout the entire frequency range from 0.008 to 0.25 Hz.

Although baroreceptor control of heart rate is well recognized, only in the work of Scher et al, (1972)[15] has an attempt been made to quantify the dynamic frequency response of this control in terms of gain and phase characteristics, with arterial pressure as the input variable. By periodic inflation of a cuff occluder on the ascending aortic arch, Scher et al. generated oscillatory intravascular arterial pressure changes (presumably at both the arch and carotid baroreceptors) in unanesthetized canines. Oscillatory reflex changes in heart interval were measured and the following gain and phase values reported: 0.027 sec/mmHg and 0^{o} at 0.06 Hz, 0.026 sec/mmHg and 20^{o} at 0.14 Hz, and 0.017 sec/mmHg and 40^{o} at 0.25 Hz. Noting that heart rate rather than heart interval was measured in the present study, and allowing for an

approximate 180^{o} phase shift in the conversion from one to the other, it can be seen that the data of Scher et al. are qualitatively similar to the present results (Figure 19), i.e. there is a progressive decrease of gain and increase in phase lag from 0.06 to 0.25 Hz. For the range of frequencies examined in the present study (0.008 - 0.25 Hz), the relative HR response to AP as the input variable (Equation 7-8) could be accounted for with a proportional-plus-derivative sensitive critically-damped second-order controller with time lag. This model yielded a good fit to both the amplitude and phase data, with some inaccuracy of the predicted amplitude below 0.02 Hz. The modeled input/output time lag of 0.626 sec is well within the 0.4 - 1.2 sec delay range reported previously[6,14] for heart rate response to step changes in carotid sinus pressure.

Results of the present study indicate that during whole body acceleration loadings, changes in stroke flow are influenced primarily by changes in heart rate (HR) and right heart filling pressure (DRVP). Comparing DRVP response in Figure 8 and blocked SF response in Figure 12, it can be seen that while DRVP amplitude and phase, and SF amplitude are roughly constant throughout the frequency range from 0.008 to 0.25 Hz, SF phase exhibits a progressive phase lag at higher frequencies. This was modeled as a simple proportional-gain plus time-lag response, in Equation 7-9. The derived time lag of 2.18 sec is in good agreement with the right-to-left heart lag of at least three cardiac cycles reported by Franklin et al. (1962)[37] for a rapid right atrial injection of saline. Assuming that there is a comparable quantitative relationship between DRVP changes and SF, and changes in left heart filling pressure and stroke volume, it can be noted that

the derived gain of roughly 0.12 (ml/b)/mmHg from Equation 7-9 is in the low range of values 0.12 - 0.36 (ml/b)/mmHg reported by Scher et al. (1968)[38] for stroke volume changes caused by changes in left ventricular filling pressure. Looking next at the nonblocked SF response (Figure 12), it can be seen that the nonblocked SF amplitudes are considerably larger than for the blocked case, while there is little difference in the phase angle responses. A comparison of nonblocked SF phase with nonblocked HR phase (Figure 11) indicates an approximate 180^{o} phase difference for most of the frequency range from 0.008 to 0.25 Hz. Considering this phase difference, and noting the reciprocal relationship between changes in heart rate and stroke volume, the difference between nonblocked and blocked SF amplitude can be attributed to the influence of HR oscillations in the nonblocked state.

In summary, the present study has demonstrated the applicability of whole body acceleration as a noninvasive stimulus for the study of integrated baroregulatory function in the normal intact cardiovascular system. In addition, the importance of the frequency range below 0.25 Hz in the characterization of the dynamic frequency response of individual cardiac and vascular barostatic control mechanisms has been shown. Finally, while the transfer relationships derived herein to describe the action of the major barostatic control mechanisms are not functionally detailed, they should provide a sound basis for the development of a practical (i.e. manageable) integrated cardiovascular control model.

CHAPTER IX

CONCLUSIONS

A number of general conclusions may be drawn from the results of the present study:

1. Sinusoidal whole body spinal-axis acceleration is a suitable noninvasive stimulus for the study, evaluation and quantification of dynamic integrated barostatic cardiovascular regulation, using classical Systems Analysis techniques. This is primarily because oscillatory intravascular pressure disturbances, produced by sinusoidal whole body acceleration, elicit significant oscillatory responses from the major cardiac and vascular barostatic control mechanisms, thus enabling the use of "describing function" analysis to quantitatively represent the frequency response characteristics of these mechanisms.

2. The dynamic (oscillatory) frequency response of the major neurally-mediated baroreflex mechanisms is limited primarily to the frequency range below 0.25 Hz.

3. During whole body acceleration a significant degree of effective dynamic barostatic regulation is achieved only at frequencies below 0.1 Hz.

4. The ability of the "closed loop", integrated baroreflex system to minimize or counteract acceleration-induced arterial blood pressure changes is less than would be predicted from previous studies of the "open loop" baroreceptor/arterial pressure response.

5. Effective barostatic regulation below 0.02 Hz is achieved principally through reflex action of systemic vascular mechanisms, through combined action of cardiac and vascular mechanisms from 0.02 to 0.04 Hz, and principally via the cardiac mechanisms from 0.04 to 0.10 Hz.

6. The frequency response characteristics of the systemic vascular mechanisms can not be accounted for with a simple first or second-order control model, with aortic arch pressure as the input.

7. The low frequency dynamics of heart rate control can be satisfactorily modeled as a proportional-plus-derivative sensitive, critically-damped second-order time lag response, using aortic arch pressure as the input variable (Equation 7-8).

8. Stroke flow is passively controlled, primarily through changes in right heart filling pressure (venous return) and heart rate, rather than by direct neural factors or changes in arterial output impedance (aortic pressure).

Finally, several recommendations are made to improve the animal preparation and experimental design for future studies of this type:

1. Since the results of the present study indicate a strong influence of venous pressure changes on the response of cardiac output during whole body acceleration, the animal instrumentation should be expanded to include vena caval or pulmonary artery flow in order to directly measure the time course of, and balance between right and left heart output during this type of cardiovascular stress.

2. In addition, provisions should be made to measure carotid sinus pressure as well as aortic arch pressure. This would allow a comparison of the pressure input to the two baroreceptor groups, thus facilitating

the development of a suitable input pressure variable for the modeling of the neurally-mediated systemic vascular responses.

NOMENCLATURE

AP	aortic arch pressure, mm Hg
LVP	left ventricular pressure, mm Hg
RVP	right ventricular pressure, mm Hg
DRVP	diastolic right ventricular pressure, mm Hg
AF	ascending aortic flow, L/min
HR	heart rate, beats/min
SF	stroke flow, ml/beat
ACC	spinal axis acceleration, G_z
G_p	proportional gain coefficient, units of output variable/ units of input variable
G_d	derivative gain coefficient, units of output variable/units of time derivative for input variable
ζ	damping coefficient, dimensionless
ω	circular frequency, rad/sec
ω_n	undamped natural frequency, rad/sec
τ	time delay, sec
s	complex quantity, $j\omega$
SEM	standard error of the mean

REFERENCES

1. Frazer, T.M. Human response to sustained acceleration. NASA SP-103: 10, 1966.

2. Gauer, O.H. and G.D. Zuidema. Gravitational Stress in Aerospace Medicine. Little Brown and Company, Boston: 16, 1961.

3. Gauer, O.H. and H.L. Thorne. Postual changes in the circulation in Handbook of Physiology. Sec. 2 Vol. 3: Circulation (Dow and Hamilton, eds.), William and Wilkins Company, Baltimore: 2409, 1965.

4. Musgrave, F.S., F.W. Zechman and R.C. Mains. Comparison of the effects of 70^{0} tilt and several levels of lower body negative pressure on heart rate and blood pressure in man. Aerosp. Med. 42 (10): 1065, 1971.

5. Peterson, D.F., V.S. Bishop and H.H. Erickson. Cardiovascular changes during and following 1-minute exposure to + G_z stress. Aviat. Space Environ. Med. 46 (6): 755, 1975.

6. Allison, J.L., K. Sagawa and M. Kumada. An open loop analysis of the aortic arch barostatic reflex. Am. J. Physiol. 217 (6): 1576, 1969.

7. Grodins, F.S. Control Theory and Biological Systems. Columbia University Press, New York: 188, 1963.

8. Herndon, C.W. Servoanalysis of the cardiovascular system. Ph.D. Dissertation, University of Mississippi, 1969.

9. Ito, C.S. Nonlinear effects of carotid sinus pressure changes on peripheral resistance. Annals New York Acad. Sci. 165:796, 1969.

10. Levison, W.H., G.O. Barnett and W.D. Jackson. Nonlinear analysis of the baroreceptor reflex system. Circ. Res. 18:673, 1966.

11. Penaz, J. and P. Burianek. Dynamic performance of vasomotor responses of resistance vessels of the carotid vascular bed in the rabbit. Arch. Int. Physiol. Biochim. 71:499, 1963.

12. Penaz, J., P. Burianek and B. Senard. Dynamic aspects of vasomotor and autoregulatory control of blood flow in Circulation in Skeletal Muscle. (O. Hudicka, ed.), Pergamon Press, Oxford: 255, 1966.

13. Scher, A.M. and A.C. Young. Nonlinearity in the control of blood pressure and heart rate. Annals New York Acad. Sci. 16:772, 1969.

14. Scher, A.M. and A.C. Young. Servoanalysis of carotid sinus reflex effects on peripheral resistance. Circ. Res. 12:152, 1963.

15. Scher, A.M., et. al. Sympathetic and parasympathetic control of heart rate in the dog, baboon and man. Federation Proc. 31:1219, 1972.

16. Scher, A.M., et. al. Studies on the carotid sinus reflex in Physical Basis of Circulatory Transport: Regulation and Exchange. (Reeve and Guyton, eds.), W.B. Saunders, Philadelphia: 113, 1967.

17. Schmidt, R.M., M. Kumada and K. Sagawa. Cardiovascular responses to various pulsatile pressures in the carotid sinus. Am. J. Physiol. 233 (1):1, 1972.

18. Stegemann, J. and U. Tibes. Sinusoidal stimulation of carotid sinus baroreceptors and peripheral blood pressure in dogs. Annals New York Acad. Sci. 16:787, 1969.

19. Skolnick, A. Crew performance requirements in the vibration envrionments of surface effects ships in Vibration and Combined Stress in Advanced Systems. AGARD CPP-145, Oslo, Norway, 1974.

20. Speakman, J.D., et al. Crew exposure to vibration in the F-4C aircraft during low-altitude, high speed flight. AMRL-TR-70-99, Aerospace Medical Research Laboratory, Wright-Patterson Air Force Base, Dayton, Ohio, 1971.

21. Bhattacharya, A. Modification of Cardiac function by heart-synchronous whole body vibration applied to awake, chronically-instrumented canines. Ph.D. Dissertation, University of Kentucky, Lexington, Kentucky 1975.

22. Edwards, R.G., E.P. McCutcheon and C.F. Knapp. Cardiovascular changes produced by brief, whole-body vibration of animals. J. Appl. Physiol. 32(3):386, 1972.

23. Von Gierke, H.E. and N.P. Clarke. Effects of vibration and buffetting on man in Aerospace Medicine. 2nd edition. (H.W. Randel ed.) Williams and Wilkins Company, Baltimore: 108, 1971.

24. Erickson, H.H. and J.R. Ritzman. Cardiovascular responses to repetitive and combat maneuvering acceleration. Proceedings of the 1975 Annual Scientific Meeting of the Aerospace Medical Association, San Francisco: 24, 1975.

25. Gillingham, K.K., J.H. Freeman and R.C. McNee. Transfer functions for eye-level blood pressure during + G_z stress. Aviat. Space Environ. Med. 48(11): 1026, 1977.

26. Sagawa, K., M. Kumada and L.P. Schramm. Nervous control of the circulation in Cardiovascular Physiology (A.C. Guyton and C.E. Jones, eds). MTP International Review of Science, Physiology Series One, University Press Park, Baltimore: 197, 1974.

27. Guyton, A.C., T.C. Coleman and T.C. Granger. Circulation: Overall regulation. Ann. Rev. Physiol. 34: 13, 1972.

28. Sagawa, K. The use of control theory and systems analysis in cardiovascular dynamics in Cardiovascular Fluid Dynamics, Vol. 1 (D.K. Bergel, ed.) Academic Press, New York: 115, 1972.

29. Korner, P.I. Integrative neural cardiovascular control. Physiological Reviews. 51(2): 315, 1974.

30. Smith, O.A. Reflex and central mechanisms involved in the control of the heart and circulation. Ann. Rev. Physiol. 36: 93, 1974.

31. Ead, H.W., J.H. Green and E. Neil. A comparison of the effects of pulsatile and non-pulsatile and blood flow through the carotid sinus on reflexogenic activity of the sinus baroreceptors in the cat. J. Physiol. 118: 509, 1952.

32. Angel James, J.E. and M.B. Daly. Comparison of the reflex vasomotor responses to seperate and combined stimulation of the carotid sinus and aortic arch baroreceptors by pulsatile and nonpulsatile pressure in the dog. J. Physiol. 209: 257, 1970.

33. Glick, G. and E. Braunwald. Relative roles of the sympathetic and parasympathetic nervous system in the reflex control of heart rate. Circ. Res. 16: 363, 1965.

34. Warner, H.R. and A. Cox. A mathematical model of heart rate control by sympathetic and vagus efferent information. J. Appl. Physiol. 17: 349, 1962.

35. Scher, A.M., A.C. Young and T.H. Kehl. The regulation of stroke volume in the resting, unanesthetized dog. Comp. Biomed. Res. 1: 315, 1968.

36. Herndon, C.W. and K. Sagawa. Combined effects of aortic and right atrial pressures on aortic flow. Am. J. Physiol. 217: 65, 1969.

37. Franklin, D.L., R.L. Van Citters and R.F. Rushmer. Balance between right and left ventricular output. Circ. Res. 10: 17, 1962.

38. Basar, E. and C. Weiss. Analyse des frequenzganges druckinduzierter anderungen des stromungswieder standes isolierter rattennieren. Pflugers Arch. 304: 121, 1968.

39. Spelman, F.A. The low frequency dynamics of the external iliac arterial bed in the unanesthetized baboon. Ph.D. Dissertation, University of Washington, Seattle, Washington, 1975.

40. Taylor, M.G. Use of random excitation and special analysis in the study of frequency-dependent parameters of the cardiovascular system. Circ. Res. 18: 585, 1966.

41. McCutcheon, E.P. and H.L. Stone. Introduction, the significance of chronically implanted instrumentation in Chronically Implanted Cardiovascular Instrumentation. (E.P. McCutcheon, ed). Academic Press, New York: 3, 1973.

42. McCutcheon, E.P., J.M. Evans and F.H. Wibel. A fabric pouch for maintenance of multiple chronically implanted lead terminations. Proceedings 4th Annual Meeting, BME Society, Los Angeles, 1973.

43. Evans, J.M., C.F. Knapp and T.R. Lowery. Pressor response buffering by beta adrenergic and cholinergic vasodilation in tranquilized dogs. Submitted for publication in Am. J. Physiol. Manuscript No. H30-8R1, May 1978.

44. Knapp, C.F. Response of the cardiovascular system to vibration and combined stress. Annual Progress Report, Air Force Office of Scientific Research Contract No. F44260-74-C-0012, 1976-77.

45. Frazier, F.E. Heart rate response of conscious canines to low frequency (<1Hz) whole-body sinusoidal acceleration. MS Thesis, University of Kentucky, 1978.

46. Richards, P.I. Computing reliable power spectra. IEEE Spectrum: 83, Jan. 1967.

47. Oppenheim, A.V. and R.W. Schafer. Digital Signal Processing. Prentice-Hall, Inc., New Jersey: 305, 1975.

48. Bruning, J.L. and B.L. Kintz. Computational Handbook of Statistics, (2nd ed.) Scott, Foresman and Company, Glenview, Illinois: 18, 1977.

49. Harrison, H.L. and J.G. Bollinger. Introduction to Automatic Controls. International Textbook Company, Scranton, Pennsylvania: 331, 1969.

50. Camill, P., C.F. Knapp and J. Collins. Computer modeling of whole body sinusoidal acceleration on the cardiovascular system. Proceedings of the 9th Annual IEEE Region III Convention: 25, 1971.

51. McLeod, J. PHYSBE.... A physiological simulation benchmark experiment. Simulation 7 (6): 324, 1966.

52. Beneken, J.E. and B. DeWit. A physical approach to hemodynamic aspects of the human cardiovascular system in Physical Basis of Circulatory Transport (E.B. Reeve and A.C. Guyton, eds.), W.B. Saunders, Philadelphia, 1967.

53. Dick, D.E. A hybrid computer study of maor transients in the canine cardiovascular system. Ph.D. Dissertation, University of Wisconsin, 1968.

54. Conley, S.W. Software design for simulation and instrumentation. Ph.D. Dissertation, University of Arizona, 1977.

55. Mancia, G., J.T. Shepherd and D.E. Donald. Interplay among carotid sinus, cardiopulmonary, and carotid body reflexes in dogs. Am. J. Physiol. 230(1): 19, 1976.

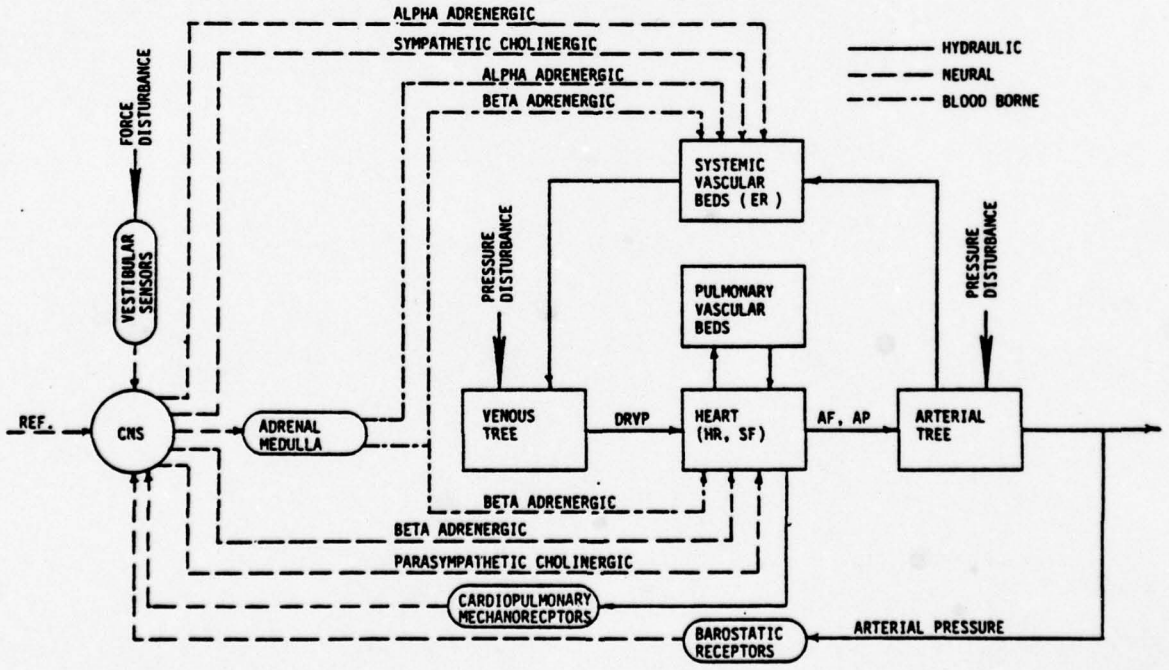
56. Uchida, Y. Afferent sympathetic nerve fibers with mechanoreceptors in the right heart. Am. J. Physiol. 228(1): 223, 1975.

57. Katona, P.G. Computer simulation of the blood pressure control of heart period.. Sc.D. Thesis, Massachusetts Institute of Technology, 1965.

RESPONSES OF THE HEART DENERVATED ANIMAL

INTRODUCTION

Cardiovascular regulation in response to acceleration stress is produced by two major mechanisms:one associated with peripheral vascular changes and the other with inotropic and chronotropic responses of the heart. Time dependent acceleration loading is translated by the inertial aspects of the musculoskeletal, fluid and vessel system into force and pressure disturbances throughout the heart and vasculature. The pressure disturbances add to or subtract from the existing pressure of the system and initiate regulatory activity as illustrated below. The present concept of cardiac and peripheral vascular control is as follows: when pressure falls at the arterial and venous pressure receptors, there is a decrease in the frequency of afferent sensory



SCHEMATIC OF THE BAROSTATIC CONTROL SYSTEM FOR RESPONSE TO ACCELERATION-INDUCED PRESSURE DISTURBANCES IN THE CARDIOVASCULAR SYSTEM.

impulses projecting into the brainstem. This causes a reflex decrease in motor activity in the cardiac branches of the vagus nerve (innervating the SA and A-V nodes) and an increase in motor activity in the sympathetic nerves which run a) to the heart and b) to the peripheral vessels, including arterioles and venous vessels, in many vascular beds. The decreased vagal activity and increased sympathetic firing act synergistically, but not necessarily simultaneously (cholinergic and beta adrenergic activity, repectively), to produce an increase in heart rate and an increase in contractility of the heart, resulting in an increase in cardiac output. The sympathetic discharge to the periphery (due to α and β adrenergic, and cholinergic activity) will produce a net increase in peripheral resistance, while constriction of the veins increases venous return and ventricular filling, leading to an increased stroke volume. All of these factors tend to increase the blood pressure and counteract the initial hypotension at the baroreceptors. With an increase in pressure at the baroreceptors, all of the sensory and motor changes described above will be of opposite sign and again the blood pressure will be returned toward normal.

The dual activation of both peripheral and cardiac efferent activity in response to acceleration stress disguises the contribution from either mechanism separately and for that reason a preparation was sought which would allow for delineation of these reactions. For this reason, we developed a canine preparation that included a totally denervated heart thereby permitting a detailed analysis of the peripheral vascular contribution to barostatic regulation.

ANIMAL PREPARATION

The procedures for total surgical cardiac denervation which we are now using differ from those reported in our earlier work in that

only a single left thoractomy is required, rather than the original 2-stage procedure. The key to the success of the operation is that the efficacy of the denervation is confirmed prior to closure of the animal's chest by demonstrating the complete absence of change in atrial and ventricular contractile force and heart rate during stimulation of the left and right thoracic vagi and left and right stellate ganglia, all of which can be visualized through a left thoracic incision. The essence of the operation is to interrupt all small nerves coursing towards the heart by completely dissecting around the great arteries, particularly the pulmonary artery, and the right and left superior pulmonary veins. The superior vena cavae must also be dissected free from surrounding connective tissue and the azygous vein tied and transected. Before closing the chest, a full range of instrumentation is implanted also (aortic flow probe, left ventricular pressure gauge, pulsed doppler coronary flow probe and occluder, and right atrial cannula). Cardiac denervation is indicated in Figure 21 which contrasts the cardiovascular response of one of the cardiac denervated dogs and a normal dog to phenylephrine (a peripheral constrictor which normally elicits a reflex decrease in heart rate) and nitroglycerine (a peripheral vasodilator which normally elicits a reflex increase in heart rate). The lack of a reflex cardiac response indicates an acceptable level of cardiac denervation.

For this study, eight animals underwent the same experimental protocol as reported for the non-denervated animals in Chapter IV, page 25; where each of these animals was studied in both the reflexive and non-reflexive state.

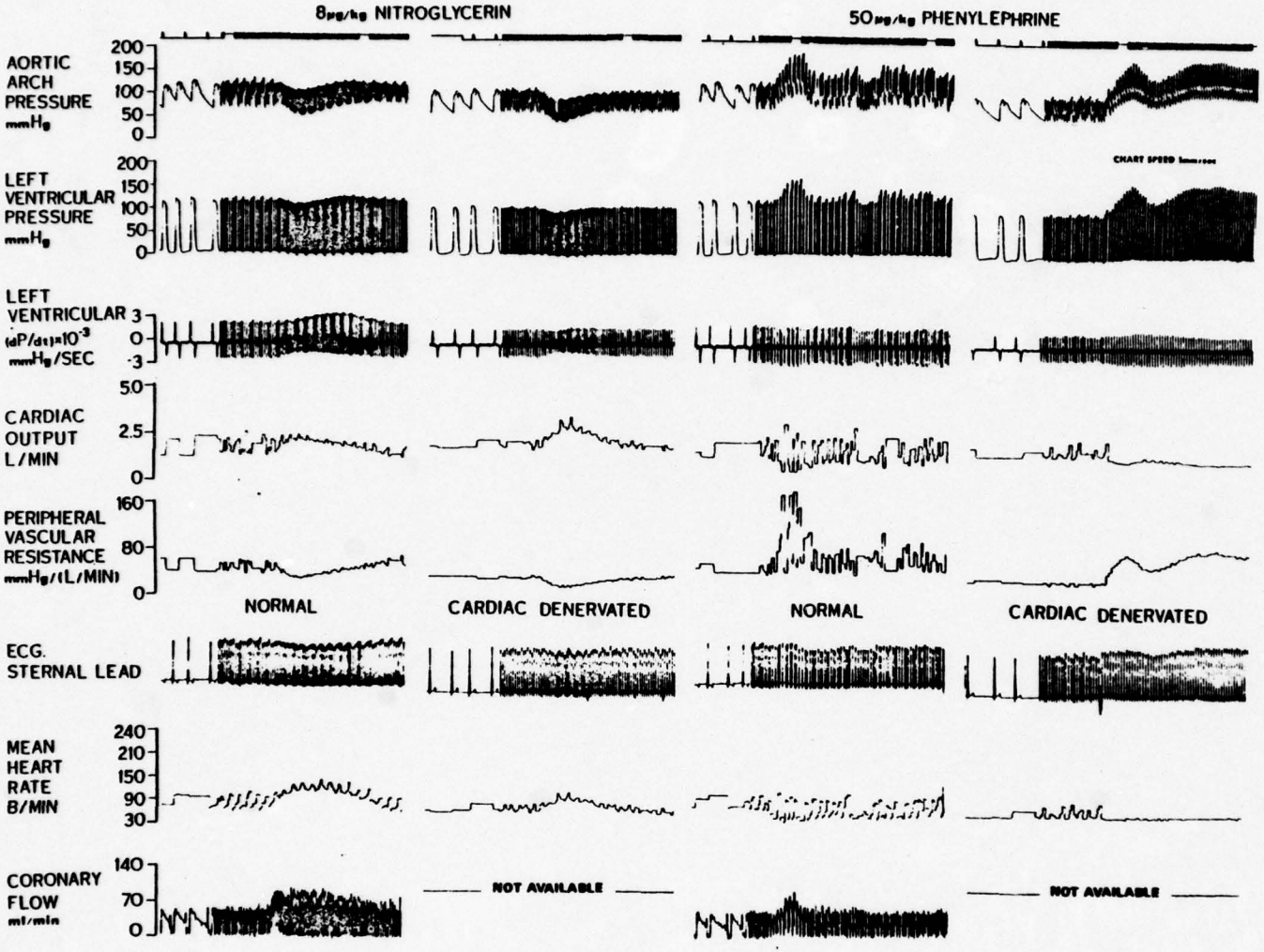


Figure 21 A comparison of the cardiovascular response to nitroglycerine (first two columns) and phenylephrine (last two columns) in a normal and a cardiac denervated animal.

RESULTS AND CONCLUSIONS

Selective cardiac denervation appeared to change the control state of these animals very little as illustrated in table 1. Reflexive aortic pressure was slightly reduced as were the arterial-to-venous pressure difference and peripheral resistance, while cardiac output, stroke volume and heart rate were slightly elevated. Total autonomic blockade reduced aortic pressure in cardiac denervated dogs (-30%) to a greater extent than it did that of normal dogs (-18%) with an increased reduction in both peripheral resistance and cardiac output.

The reflexive response of the cardiac denervated dogs to acceleration stress was however quite different from that of the reflexive, normal dog's response. Where the reflexive, normal animal was found to be able to minimize aortic pressure oscillations in the low frequency range (first column, Figure 22) with an in-phase increase in peripheral vascular resistance, the reflexive, cardiac-denervated animals were all found to have much larger oscillations in aortic pressure (Figure 23). Surprisingly these oscillations were even greater than the oscillations seen in the non-reflexive animals, either normal or cardiac denervated.

A comparison of the oscillatory aortic pressure response for the group of denervated animals to a group of normal animals is shown in Figure 24 for both groups in both the reflexive and the non-reflexive state. The non-reflexive response for both groups was quite similar, with oscillations of the order of 50 mm Hg at the lowest frequencies tapering off to 20 mm Hg oscillations at the highest frequencies. That both groups of animals had the same non-reflexive response indicated that the hydraulic aspect of the acceleration stress was the

NORMAL ANIMALS (8)

	Mean Aortic Pressure mmHg	Arterial To Venous Pressure Difference mmHg	Peripheral Vascular Resistance mmHg/(L/min)	Cardiac Output L/min	Stroke Volume ml	Heart Rate b/min
REFLEXIVE	95.1	99.4	49.2	2.12	23.8	89.0
± SEM	±6.3	±6.3	±4.0	±.10	±1.4	±8.2
NON-REFLEXIVE	77.8	80.2	39.3	2.06	15.9	129.7
± SEM	±11.9	±14.5	±5.7	±.20	±1.4	±5.9

CARDIAC DENERVATED ANIMALS (8)

REFLEXIVE	89.5	97.9	43.2	2.35	25.4	92.5
± SEM	±3.4	±2.7	±3.7	±.19	±1.3	±5.6
NON-REFLEXIVE	63.9	66.3	33.2	2.08	16.2	128.8
± SEM	±4.5	±4.5	±3.1	±.16	±1.5	±5.9

Table 1. Pre-acceleration control values for 8 normal and 8 cardiac denervated dogs in both the reflexive and non-reflexive (following total autonomic pharmacological blockade) state.

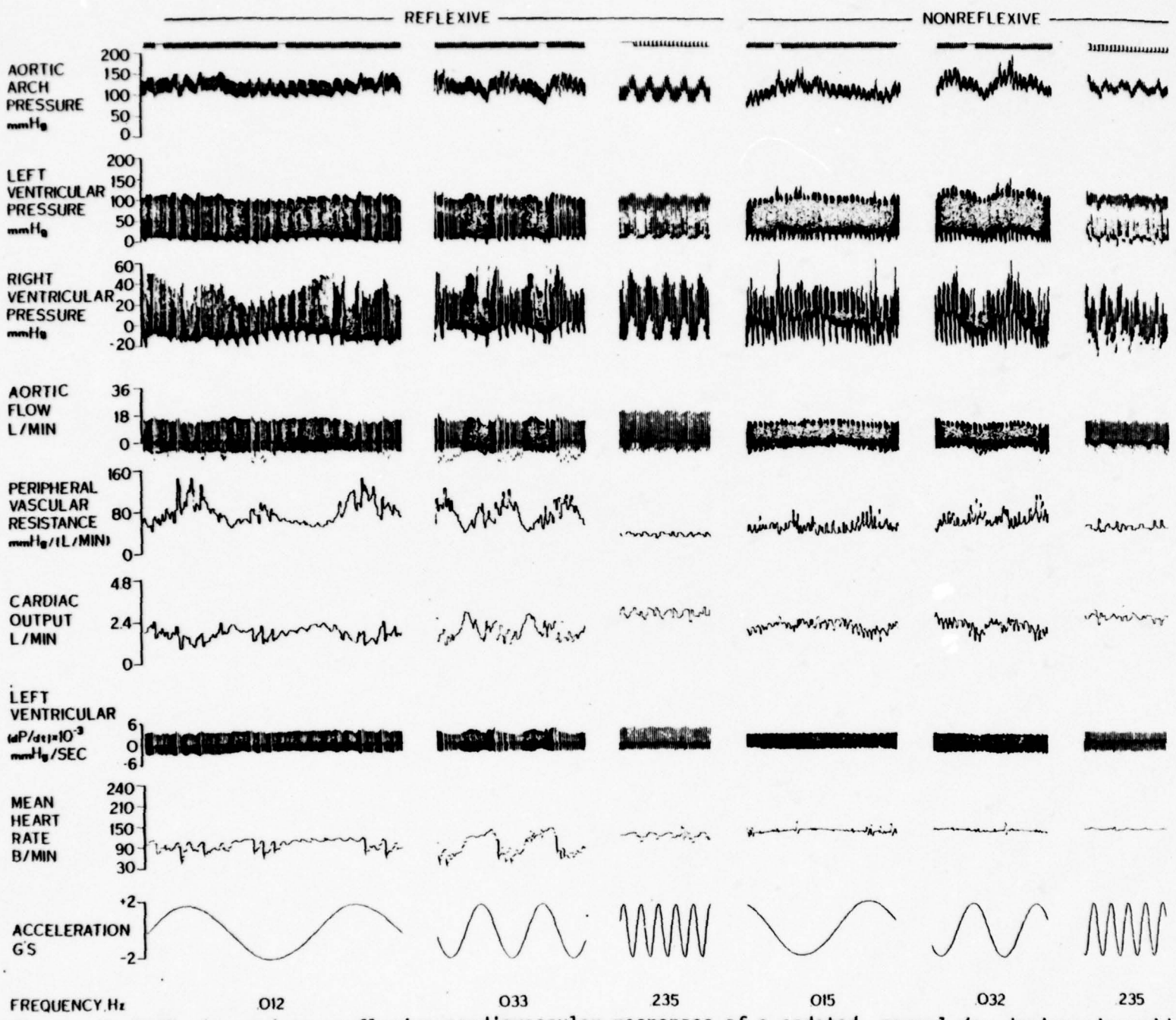


Figure 22 Reflexive and non-reflexive cardiovascular responses of a sedated, normal dog during sinusoidal ±2 g_z whole body acceleration. Traces 5 and 6 are one-beat-delayed, digitally calculated variables.

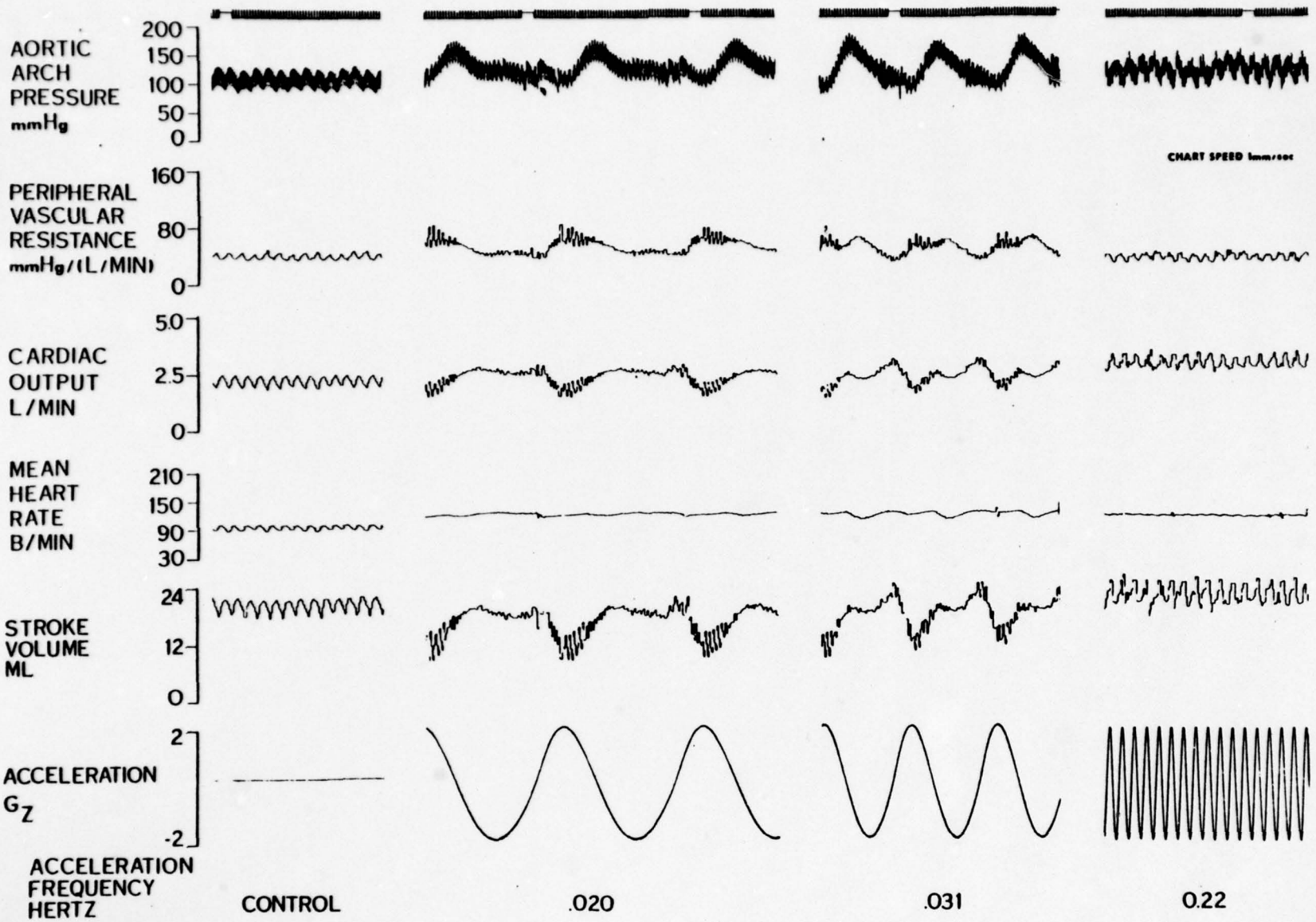


Figure 23 Reflexive cardiovascular responses of a sedated, cardiac denervated dog during sinusoidal ±2 g_z whole body acceleration. Traces 2, 3, 4 and 5 are one-beat-delayed, digitally calculated variables.

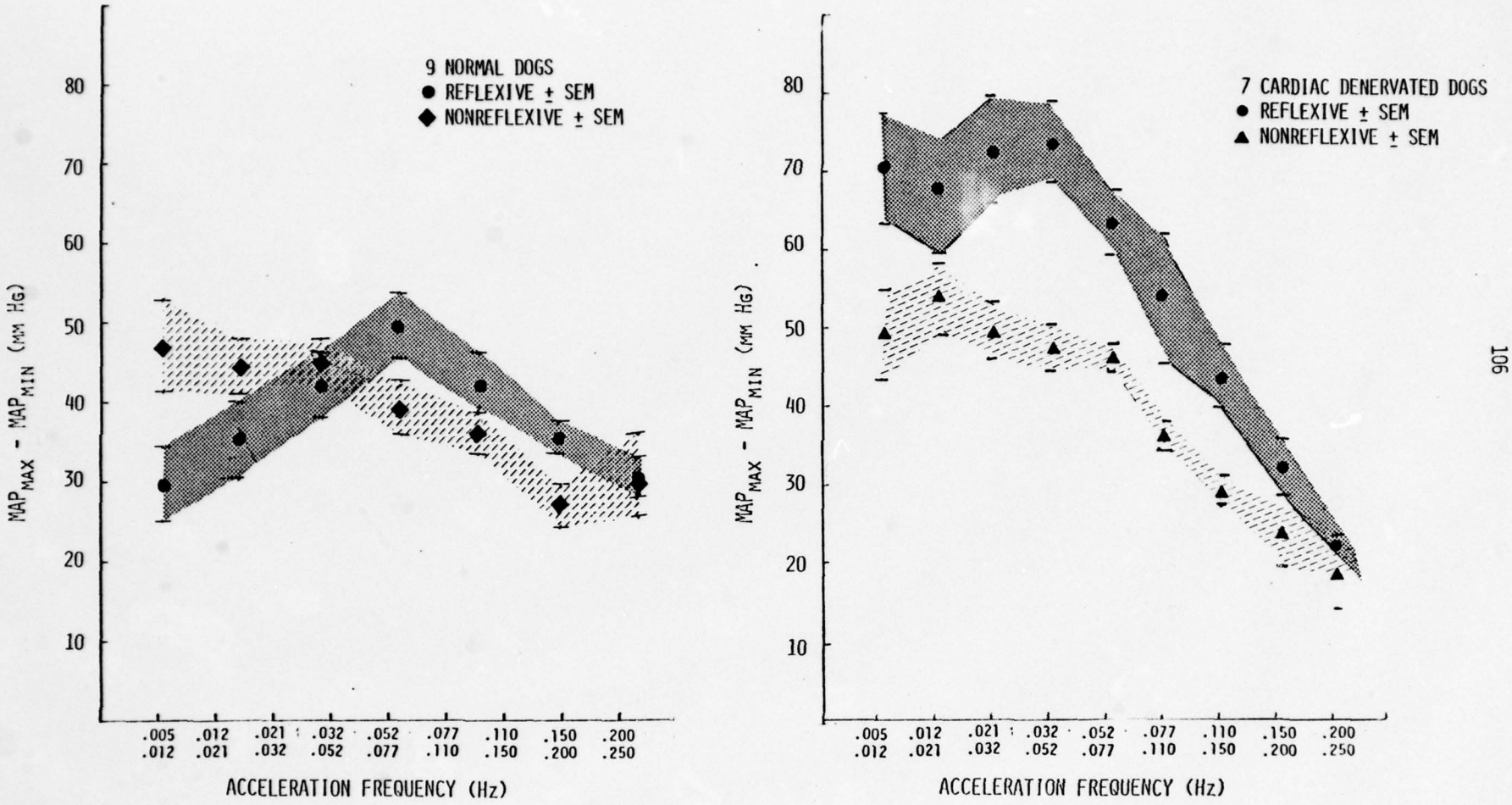


FIGURE 24 COMPARISON OF THE MAGNITUDE OF OSCILLATIONS IN AORTIC PRESSURE ACROSS THE FREQUENCY RANGE STUDIED FOR THE GROUP OF NORMAL ANIMALS (BOTH REFLEXIVE AND NONREFLEXIVE) AND THE GROUP OF CARDIAC DENERVATED ANIMALS.

same in the two groups, and therefore comparison of the groups' reflexive states was reasonable. The reflexive normal oscillations were minimal at the lowest frequency, about 30 mm Hg, peaking in the middle frequency range at about 50 mm Hg and tapering off like the hydraulic animals to about 30 mm Hg at the highest frequencies. In contrast, the reflexive cardiac denervated pressure oscillations were quite large, above 70 mm Hg across the low to middle frequency range, tapering sharply off to 20 mm Hg at the highest frequency.

Several observations were made concerning the cardiac output and peripheral resistance compents of these pressure oscillations (cf. Figures 22 and 23). In the last three columns of Figure 22, (non-reflexive normal dog) neither cardiac output nor peripheral resistance had large oscillations and what there was, was assumed to be hydraulic. In the first column (reflexive normal dog) aortic pressure was maintained constant by an in-phase increase in peripheral resistance with each +2 G_z peak. In addition, a secondary -2 G_z peak was observed that appeared to increase with increasing frequency, to become a major component of the peripheral resistance increase in the middle frequency range where the peak of aortic pressure coincided with both -2 G_z and the peak of peripheral resistance (column 2, Figure 22). At the higher frequencies (column 3 Figure 22) there was no evidence of peripheral constriction, but the mean value of cardiac output was elevated over the control value, and peripheral resistance was decreased from its control value. In the cardiac denervated cases (Figure 23) the peak of the aortic pressure oscillations at the lowest frequency appeared to correlate with neither the peak of peripheral resistance nor the -2 G_z acceleration peak, but

resulted from a high level of resistance coupled with a near peak level of cardiac output. In the middle frequency range, peak aortic pressure corresponded more closely with the -2 G_z acceleration peak and the secondary increase in peripheral vascular resistance. At the highest frequencies, oscillations in pressure, cardiac output and peripheral resistance were all minimal.

Cardiac output oscillations for both groups of animals in both the reflexive and non-reflexive states are shown in Figure 25. Again the non-reflexive, hydraulic oscillations (triangles) appeared to be of the same order of magnitude for both the normal and cardiac denervated animals; on the order of 1 L/min at the lower frequencies tapering to 0.5 L/min at the higher frequencies. The reflexive, normal animals (circles, left half Figure 25) had oscillations of above 1 L/min across the frequency range, while the reflexive, cardiac denervated animals (circles, right half, Figure 25) have larger oscillations at both the low and middle frequencies, tapering off to smaller oscillations at the higher frequencies.

Peripheral vascular resistance oscillations are shown for both the reflexive, normal animals and the reflexive, cardiac denervated animals in Figure 26. The amplitude of the peripheral resistance oscillations in the normal dogs dropped from ~ 40 mm Hg / (L/min) at the lowest frequencies to ~ 20 mm Hg / (L/min) at the highest frequencies. In the cardiac denervated dogs, the oscillations were of the same magnitude (~ 45 mm Hg / (L/min) at the low frequencies, dropping less dramatically to ~ 30 mm Hg / (L/min) at the highest frequencies. Due to the double-peaked response, that was evident in most of the animals, the magnitude of the

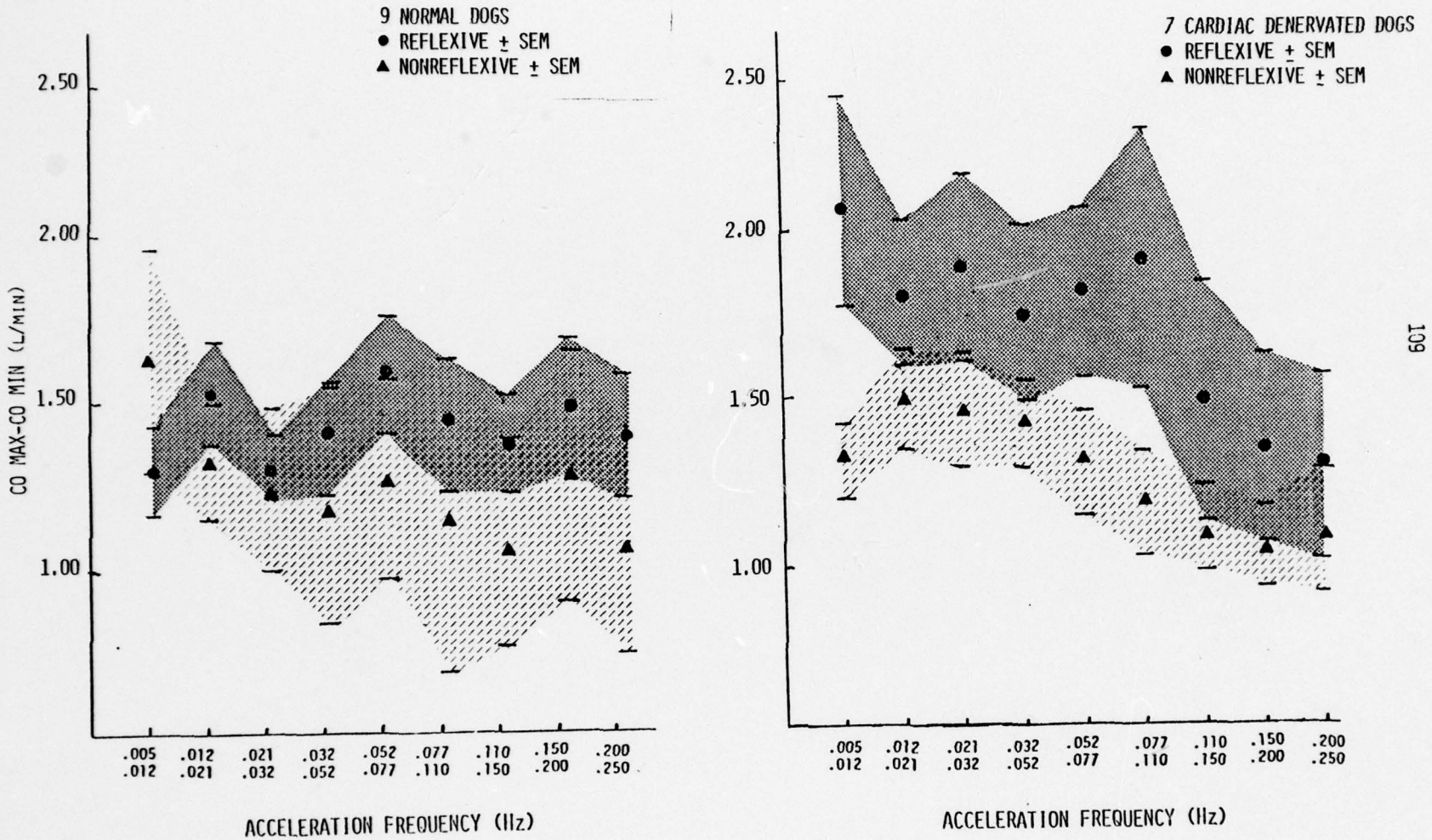


FIGURE 25 COMPARISON OF THE MAGNITUDE OF OSCILLATIONS IN CARDIAC OUTPUT ACROSS THE FREQUENCY RANGE STUDIED FOR THE GROUP OF NORMAL ANIMALS (BOTH REFLEXIVE AND NOREFLEXIVE) AND THE GROUP OF CARDIAC DENERVATED ANIMALS.

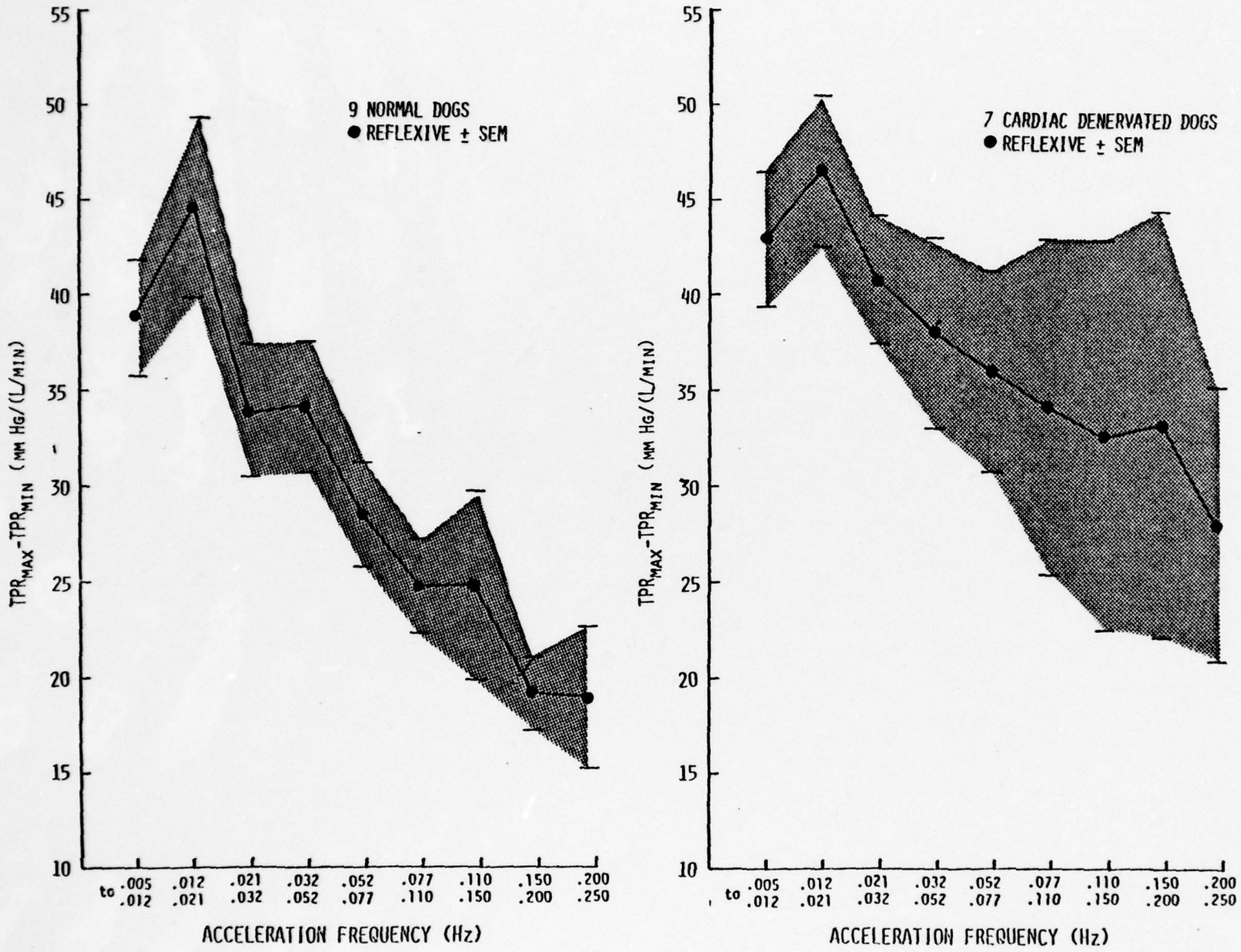
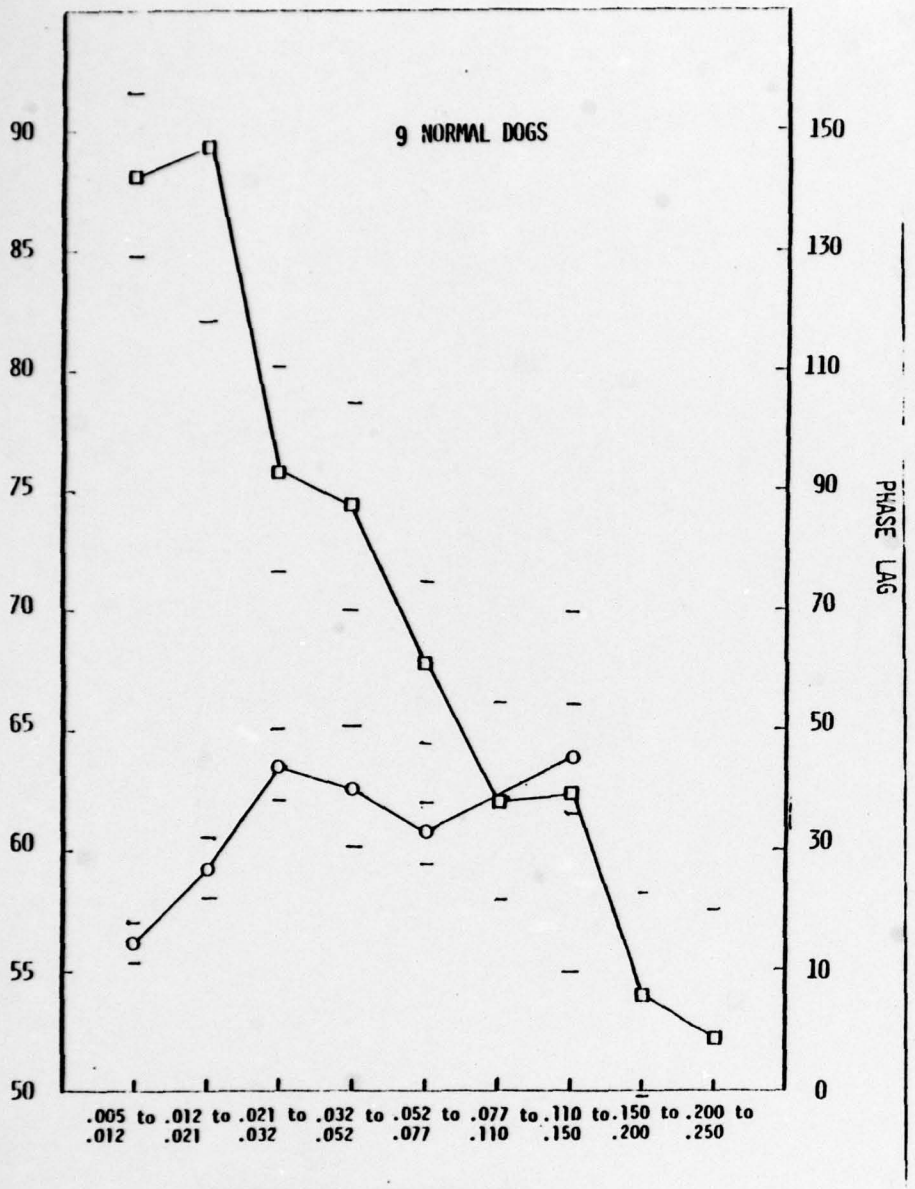


FIGURE 26. COMPARISON OF THE MAGNITUDE OF OSCILLATIONS IN PERIPHERAL RESISTANCE ACROSS THE FREQUENCY RANGE STUDIED FOR THE GROUP OF REFLEXIVE NORMAL ANIMALS AND THE GROUP OF REFLEXIVE CARDIAC DENERVATED ANIMALS.

oscillations in peripheral resistance were examined as a function of whether they occurred with the +2 G_z acceleration peak or the -2 G_z acceleration peak.

The peak values of peripheral vascular resistance associated with the +2 G_z acceleration peak and the phase relationship of this peak to the +2 G_z acceleration peak are shown for both the reflexive normal and cardiac denervated groups in Figure 27. Mixing of these two peaks makes the phase relationship difficult to determine above 0.1 Hz. The maximum value reached with +2 G_z diminishes while the lag of this peak increases with increasing frequency in both the normal and cardiac denervated animals. The similarity of these responses would appear not to implicate this part of the response as a major component of the increased oscillations in aortic pressure seen in the denervated animals at the lower frequencies. It does however appear to add to the increase in resistance with -2 G_z which had its maximum peak values in the middle frequency range.

Our conclusion from this series of studies is that the increased aortic pressure oscillations seen from .005 to 0.1 Hz in the reflexive, cardiac denervated animals as compared to the reflexive, normal animals resulted from a combination of greatly increased oscillations in cardiac output across this range and slightly increased oscillations in peripheral vascular resistance, especially above 0.02 Hz. The increased pressure oscillations in the middle frequency range appear to result from increased oscillations in both cardiac output and peripheral resistance. That the low frequency, cardiac output oscillations were considerably greater



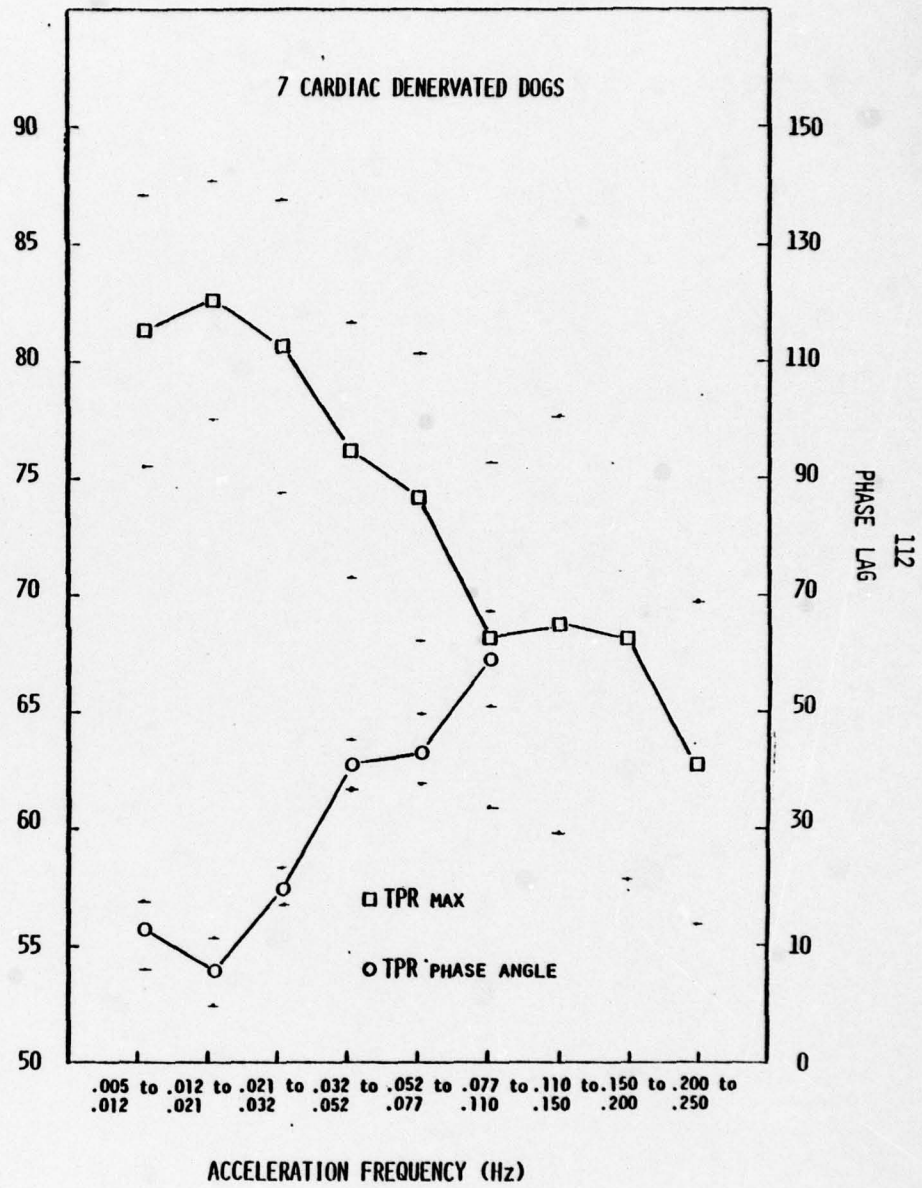


FIGURE 27 COMPARISON OF THE MAGNITUDE OF THE $+2G_z$ VALUE OF PERHIPHERAL RESISTANCE AND ITS PHASE RELATIONSHIP TO THE $+2G_z$ ACCELERATION PEAK ACROSS THE FREQUENCY RANGE STUDIED FOR THE GROUP OF REFLEXIVE NORMAL ANIMALS AND THE GROUP OF REFLEXIVE CARDIAC DENERVATED ANIMALS.

than those seen in the non-reflexive animals implies to us that in the normal, reflexive animal, cardiac afferent activity may play a significant role in regulation of cardiac output.

NEUROHORMONAL COMPONENTS OF THE ACCELERATION INDUCED PRESSOR RESPONSE IN BOTH NORMAL AND CARDIAC DENERVATED ANIMALS

Onset of the low frequency, sinusoidal acceleration used as a stressor in this study routinely produced an increase in aortic pressure, heart rate and peripheral vascular resistance, little change in left or right ventricular (diastolic) pressures, and a decrease in stroke volume and cardiac output in Innovar-sedated dogs. This pressor response was evident within the first minute of the onset of centrifugation, persisted throughout the 30 minutes of the test period, appeared to be fairly independent of the frequency of acceleration, and remained for several (10 to 15) minutes following the end of the test period. In addition, it appeared to be independent of autonomic effector activity since it was common to both normal (reflexive) dogs and dogs in which sympathetic α, β and cholinergic activity had been pharmacologically blocked (non-reflexive dogs). The magnitude of the response routinely increased aortic pressure by 20 to 30 mm Hg in reflexive dogs and by 60 to 70 mm Hg in non-reflexive dogs.

That the non-reflexive animals responded, eliminated all autonomic neural activity, including circulating catecholamines, as the source of this increased pressure. Other candidates for this particular effect were therefore considered: plasma volume shifts, plasma renin activity and/or vasopressin (ADH) activity. Since the net decrease in stroke volume was on the order of 40% in reflexive animals and 30% in the non-reflexive animals at the lowest frequencies (which also occurred at the onset of centrifugation), it was felt that activation of either renin or vasopressin

release was quite possible, and volume shifts could not be discounted. Accordingly, right artrial blood samples were withdrawn from the animals just prior to, and within the first minute following, centrifugation. Pre-and post-centrifuge samples were taken from the animal in the reflexive state and again following total autonomic blockade produced by intravenous infusion of the propranol, atropine and phenoxybenzamine. Plasma volume was determined by the RISA ^{131} technique, with subsequent changes indicated by changes in hematocrit. Plasma renin activity was determined in a routine analysis performed by the renal division of the UK Department of Medicine, and vasopressin activity was measured by a member of the renal division of the Department of Medicine at Indiana University, using a technique which also determined plasma osmolarity.

Preliminary results from these tests are shown in Figure 28 for each of these variables for a small group of animals. Vasopressor activity and hematocrit (and plasma volume) were done on the same animals, one of which was normal animal while the other three had undergone selective cardiac denervation. Plasma renin activity was measured in 5 different animals, 2 of which had undergone cardiac denervation. For all three variables there was no differnece in either control levels or centrifugation response of the cardiac denervated, as opposed to the normal, animals and their responses are therefore grouped together.

The results of the plasma renin activity measurements indicated:

A) All 5 of these dogs had low plasma renin activity, perhaps due to their sedated but not anesthetized state

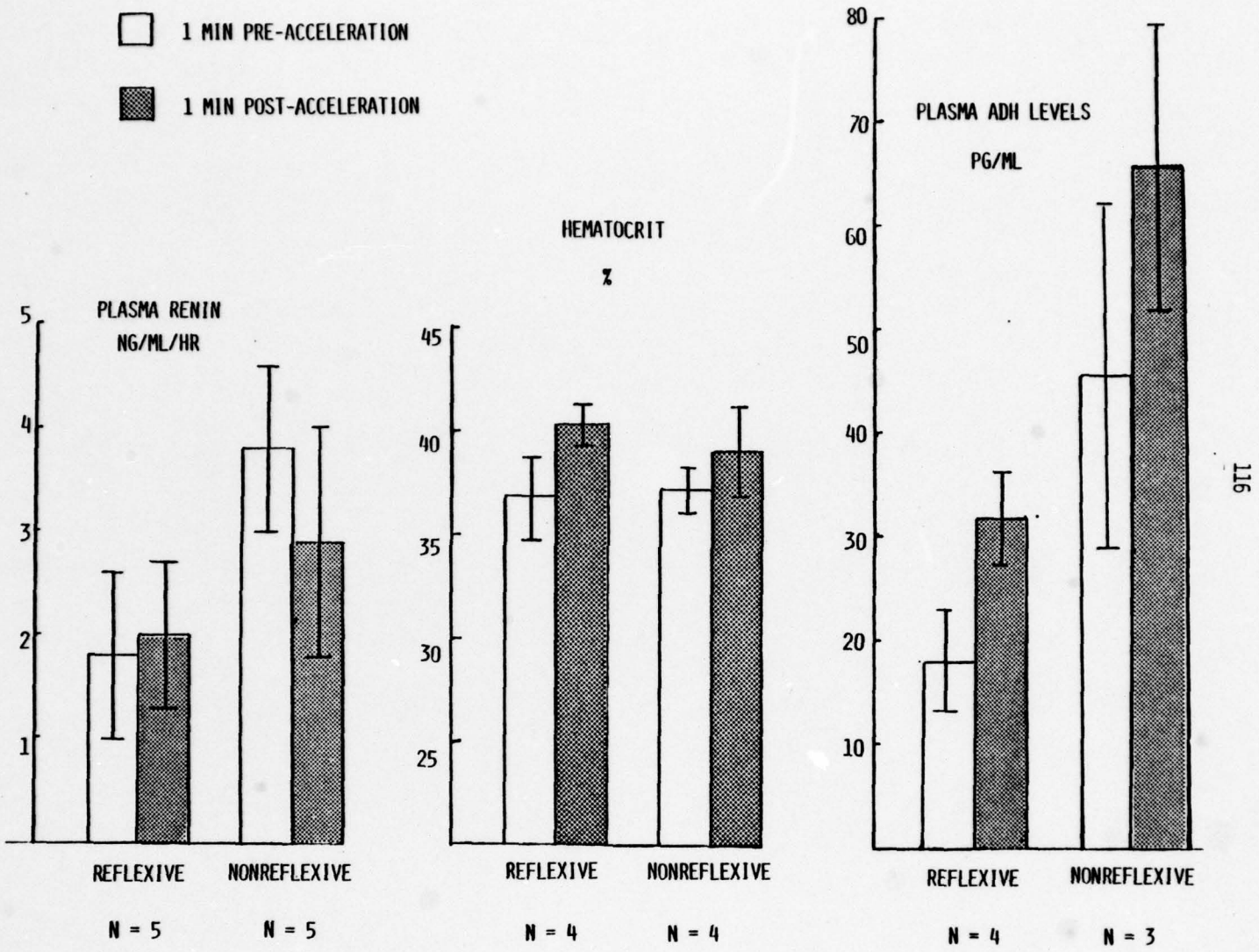


FIGURE 28 CONTROL AND TEST VALUES OF PLASMA RENIN ACTIVITY, HEMATOCRIT AND VASOPRESSIN (ADH) FOR REFLEXIVE AND NONREFLEXIVE (FOLLOWING TOTAL AUTONOMIC BLOCKADE) SEDATED DOGS.

B) Acceleration produced no consistent changes in plasma renin activity in either the reflexive or non-reflexive state

C) Total automonic blockade doubled control levels of plasma renin activity.

Hematocrit changes indicated a tendency for hematocrit to increase with acceleration in 7 out of 8 cases. This observation was not substantiated by the $RISA^{131}$ results which were felt to be unreliable after the initial measurement.

Results of the Vasopressin analysis indicated:

A) Centrifugation increased ADH levels in all animals in both the reflexive and non-reflexive state.

B) The stimulus to increase the ADH level in this study was not derived from plasma osmolarity changes, since there was no consistent change in osmolarity with centrifugation,

C) Total autonomic blockade more than doubled resting levels of ADH, but did not appear to affect the release of ADH with centrifugation

D) All animals had high levels of resting ADH, perhaps due to the sedated but not anesthetized state of the animal, and

E) The signal to increase ADH levels with centrifugation was not derived solely from low volume receptors in the heart, since three of these animals had previously undergone total cardiac denervation.

Our tentative conclusion from these preliminary results therefore is that the pressor response to sinusoidal, low frequency acceleration is due primarily to an increase in plasma vasopressin activity, triggered by the decrease in plasma volume and/or the decrease in upper body arterial and venous pressures that comes with each +2 G_z portion of the acceleration waveform.

REPORT DOCUMENTATION PAGE

READ INSTRUCTIONS BEFORE COMPLETING FORM

1. REPORT NUMBER	2. GOVT ACCESSION NO.	3. RECIPIENT'S CATALOG NUMBER
AFOSR-TR- 79-0676		

4. TITLE (and Subtitle)

The Causes of Decrements in Aircrew Performance: Physiological Changes Produced by Vibration and Other Environmental Stresses and Response of the Cardiovascular System to Vibration & Combined Stress.

5. TYPE OF REPORT & PERIOD COVERED

1973-1978 Final Report

6. PERFORMING ORG. REPORT NUMBER

1973-1978

7. AUTHOR(s)

Knapp, C. F. — Charles F. Knapp
Evans, J. M. — J. M. Evans
Randall, D. R. — D. R. Randall

8. CONTRACT OR GRANT NUMBER(s)

F44620-74-C-0012

9. PERFORMING ORGANIZATION NAME AND ADDRESS

Wenner-Gren Research Laboratory
University of Kentucky
Lexington, Kentucky 40506

10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS

61102F
2312A2
A2

11. CONTROLLING OFFICE NAME AND ADDRESS

Air Force Office of Scientific Research (NL)
Bolling AFB DC 20332

12. REPORT DATE

Sept[illegible]978

13. NUMBER OF PAGES

145

14. MONITORING AGENCY NAME & ADDRESS *(if different from Controlling Office)*

147p

15. SECURITY CLASS. *(of this report)*

Unclassified

15a. DECLASSIFICATION/DOWNGRADING SCHEDULE

16. DISTRIBUTION STATEMENT *(of this Report)*

Approved for public release; distribution unlimited.

17. DISTRIBUTION STATEMENT *(of the abstract entered in Block 20, if different from Report)*

18. SUPPLEMENTARY NOTES

19. KEY WORDS *(Continue on reverse side if necessary and identify by block number)*

Cardiovascular Response to Acceleration Stress, Chronically Instrumented Canines, Whole Body Sinusoidal Acceleration, Low Frequency Acceleration, Centrifuge.

20. ABSTRACT *(Continue on reverse side if necessary and identify by block number)*

A. PROGRAM SUMMARY 1973-1978

The goal of this program is the understanding of cardiovascular responses to whole body, low frequency, sinusoidal acceleration loading of the intact physiological system. Our efforts in the early phase of the

408 012

DD FORM 1 JAN 73 1473

UNCLASSIFIED

SECURITY CLASSIFICATION OF THIS PAGE *(When Data Entered)*

20. (continued)

program were limited to investigating cardiovascular responses to high frequency whole body acceleration (2-30Hz), but more recently have been extended to the domain between sustained and time-varying acceleration of less than 1 Hz. Results from the early phase indicated that whole-body acceleration in the 2-30Hz range produced an exercise-type response that was directly dependent on the force level applied. Mean heart rate, stroke volume, cardiac output and whole body oxygen consumption were found to be linearly dependent on the peak net force delivered to each animal. Results from the later phase of this study indicated that whole body acceleration in the .005 to 0.25Hz range included a resonance-type phenomenon in which the neural regulatory systems appeared to be unable to regulate arterial pressure in the middle portion of this frequency range.